ANNALS OF INTERNAL MEDICINE

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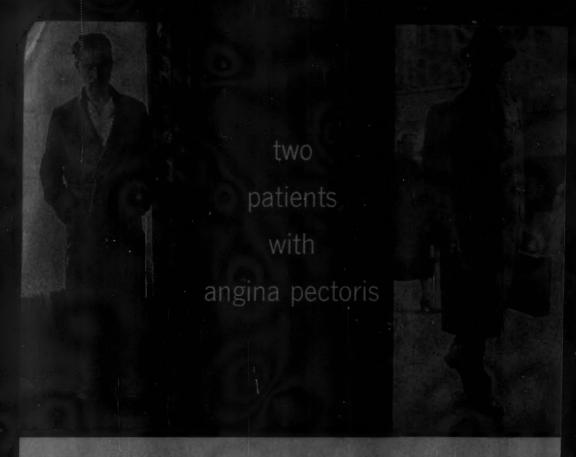
VOL. 45, NO. 6



DECEMBER, 1956

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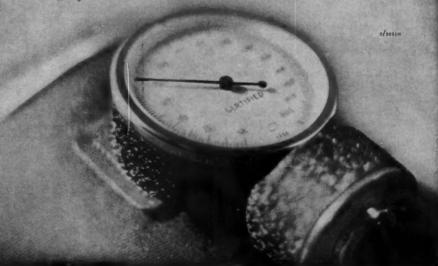
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1. Plummer, A. J., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E.: J. Pharmacol, & Exper, Therap. 115-172 (Oct.) 1955. 2. Grimson, K. S.: J.A.M.A. 158:359 [June 4] 1955. 3. Smith, J. R., and Hoobler, S. W.: Univ. Michigan M. Bull. 22:51 [Feb.] 1956. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation 11:733 (May) 1955.

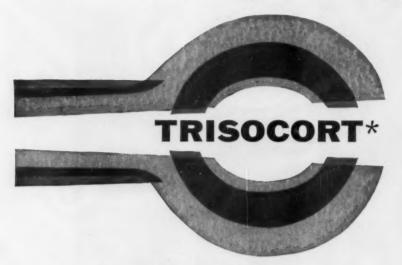
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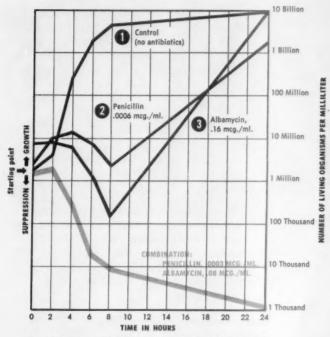
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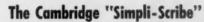
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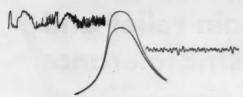
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- Doyle, P. J., and Livingston, S.: J. Pediat. 43:413 (Oct.) 1953.
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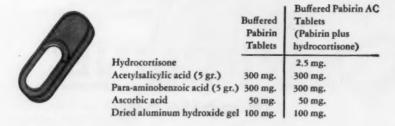
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1. Hardin, J. H.; Levy, J. S., and Seager, L.: South. M. J. 47:1190,1954.

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THE CASE FOR EARLY CONTROL OF HYPERTENSION'

In the Guest Editorial for GP in July, Dr. Edward D. Freis reexamines two major questions:

1. Should Hypertension Be Treated Early?

Freis finds the case for early treatment to rest on cause-and-effect evidence: "... high pressure, ... and nothing else but this high pressure, creates many if not all the organic manifestations that lead to the final disability and eventual death of the patient." The "evidence presents a cogent argument for the treatment of hypertension early before vascular damage has occurred."

2. What Is the Role of the More Potent

Agents? "... the evidence... suggests that the technique [for the effective and safe use of such agents as ANSOLYSEN] should be more widely learned and employed. Furthermore,... the patients with early hypertension, especially those without renal damage, are far more easily controlled, with fewer side effects, than the patients with advanced hypertension."

Freis cautions that these views are not presented as dogma; "... they have been developed to show the other side of an argument that seems to have many points in its favor."

1. Freis, Edward D.: Guest Editorial. GP 14:72 (July) 1956.

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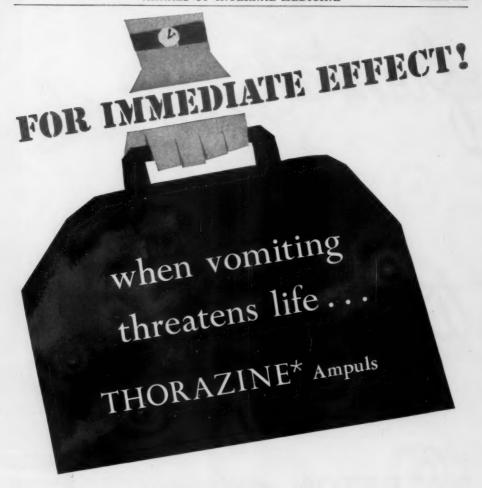
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*Ausman, D.C.: Cobalt-Iron Therapy in the Treatment of Some Common Anemias Seen in General Practice, the Journal Lancet (Oct.) 1956.

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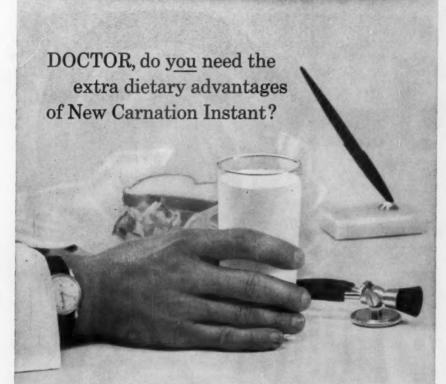
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1. Moyer, J. H., et al.: Drug Therapy of Hypertension: Preliminary Observations on the Clinical Use of Mecamylamine (A Ganglionic Blocking Agent) in Combination with Rauwolfia for the Treatment of Hypertension, Med. Rec. & Ann. 49:390 (Sept.) 1955.

1955. 2. Sturgis, C. C., et al.: Advances in Internal Medicine, J. Michigan M. Soc. 55:154 (Feb.) 1956.

*In this clinical trial all patients were given, in addition to one of the ganglionic blocking agents, a constant daily amount of reserpine.

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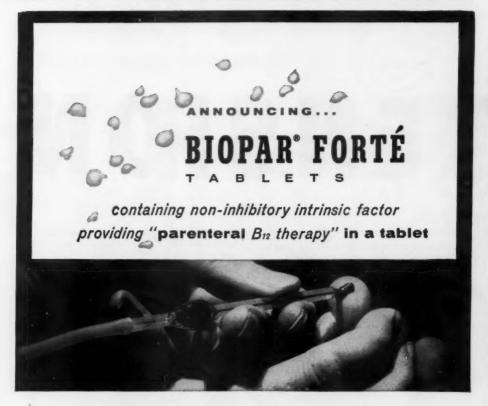


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Lemere, F.: Northwest Med. 54: 1098, 1955.

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Sokoloff, O.J.: A.M.A. Arch. Dermat. In press.

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Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. 17: 19, 1956.

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Borrus, J.C.: J.A.M.A. 157: 1596, 1955.

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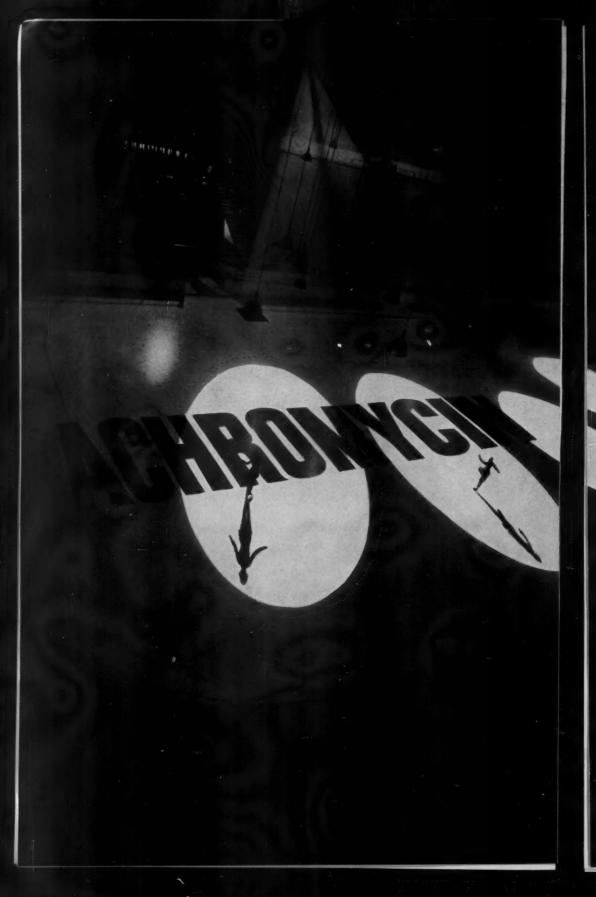
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- Prigot, A. and Marmell, M. Antibiotics and Chemotherapy 4:1117 (Oct.) 1954.
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- 4. English, A., et al.: idem 4:441 (April) 1954.



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 Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: J.A.M.A., 158:625, June 25, 1955.

2. Schwab, R.S.: Am. Jour. Med., 19:734, Nov., 1985.

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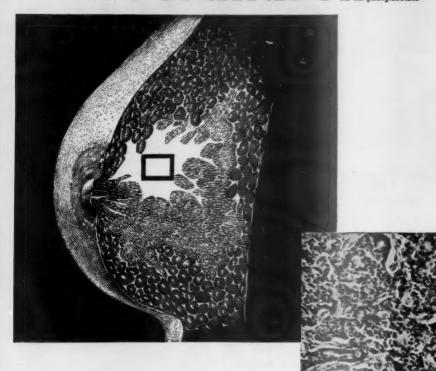


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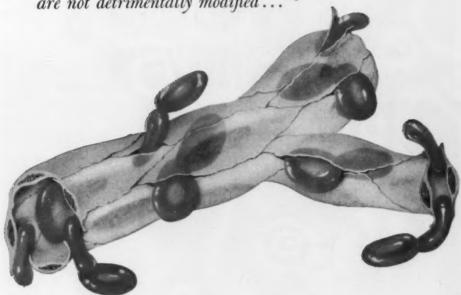
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References: 1. Martin, G. J., et al.: Exper. Med. & Surg. 12:555, 1954. 2. Griffith, J. Q., Jr., and Lindauer, M. A.: Am. Heart J. 22:758, 1944. 3. Barishaw, S. B.: Exper. Med. & Surgs. 7:358, 1949. 4. Epstein, E. Z., and Greenspan, E. B.: Arch. Int. Med. 68:1074, 1941. 5. Warter, P. J., et al.: Delaware M. J. 20:41, 1948. 6. Beaser, S. B., et al.: Arch. Int. Med. 73:18, 1944. 7. Greenblatt, R. B.: Office Endocrinology, ed. 4. Springfield, Ill., Charles C. Thomas, 1952. 8. Gale, E. T., and Thewles, M. W.: Geriatrics 8:80, 1953. 9. Drezner, H. L., et al.: Am. Pract. & Digest. Treat. 6:912, 1955. 10. Selsman, G. J. V., and Horoschak, S.: Am. J. Digest Dis. 17:92, 1950. 11. Loughlin, W. C.: New York J. Med. 49:1823, 1949.

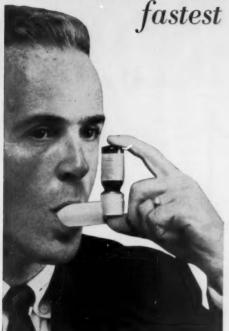
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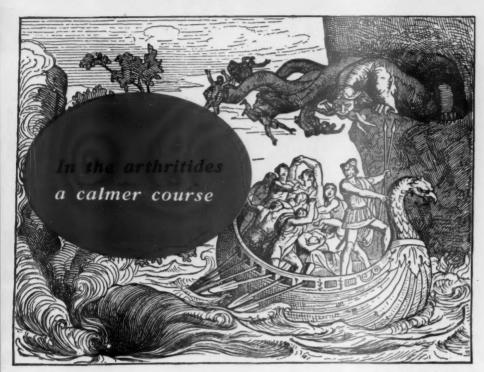
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Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105

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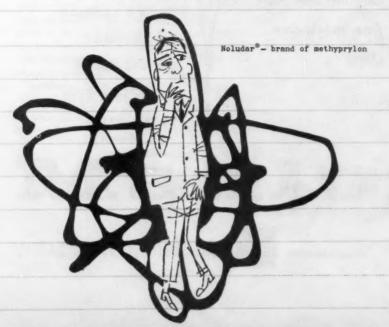
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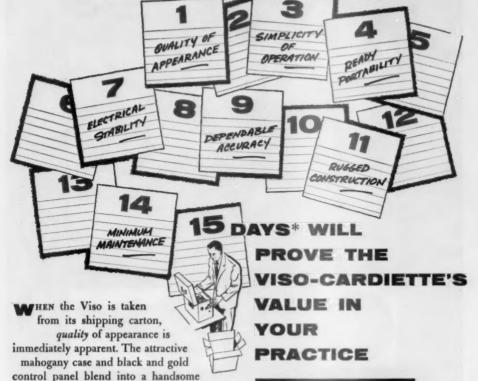


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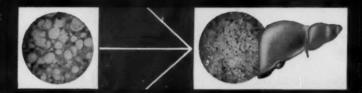
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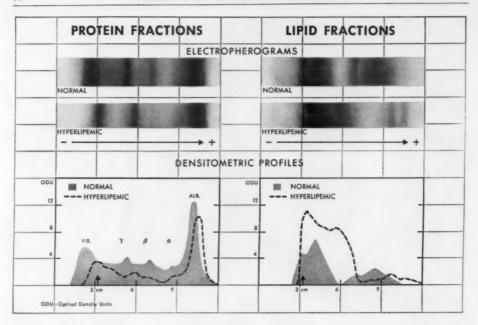
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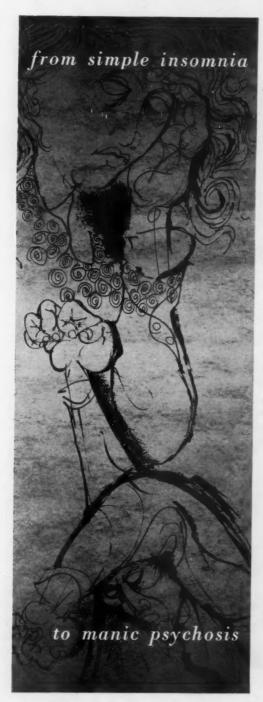
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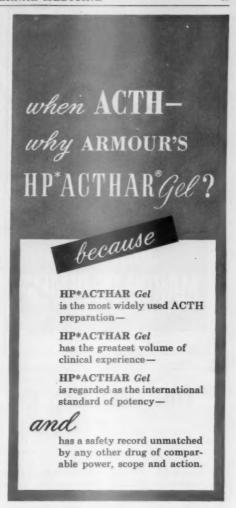


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Course No. 8, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS: Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., (Associate), and Edward H. Reinhard, M.D., (Associate), Co-directors. February 18 to 22, 1957.

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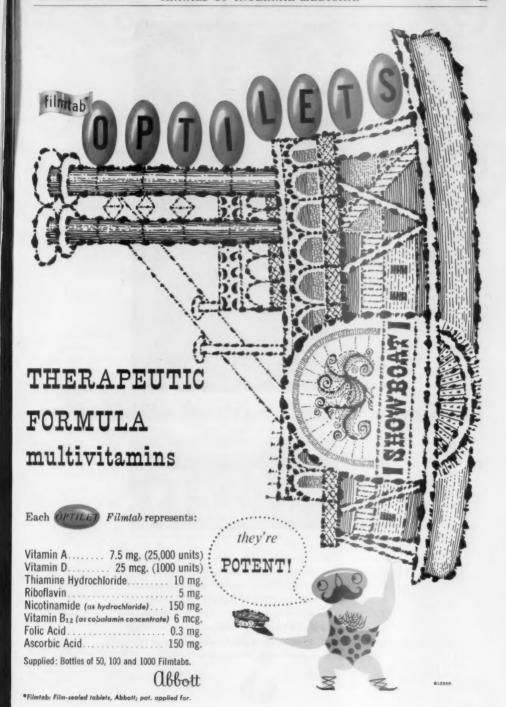
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ANNALS OF INTERNAL MEDICINE

VOLUME 45

DECEMBER, 1956

NUMBER 6

THE SURGICAL MANAGEMENT OF CORONARY ARTERY DISEASE: BACKGROUND, RATION-ALE, CLINICAL EXPERIENCES *

By CLAUDE S. BECK, M.D., and BERNARD L. BROFMAN, M.D., Cleveland, Ohio

INTRODUCTION

This presentation is based upon the direct approach to the coronary blood supply to the heart. About 5,000 experimental operations have been carried out on dogs in the last 23 years.1 The facts here presented were determined by observations made directly on the heart. What actually happened in these experiments determined the facts which make up this presentation. With this foundation the facts should have enduring value.

To illustrate how the observation of a fact destroys a preconceived idea, the following incident is cited: On June 21, 1955, a 65 year old physician had anginal pain. The next day he came to the University Hospitals of Cleveland for an electrocardiogram. On the way out of the hospital he fell over dead from a fatal heart attack. Within a few minutes his chest was opened, the heart was massaged and oxygen was delivered to his lungs. Defibrillation of the heart was achieved. Nine months later this physician is practicing medicine. After this act was accomplished several internists raised this question: "You would not have done this, would you, if you knew he had had a fatal heart attack?" Preconceived ideas must vield to

^{*} Received for publication April 20, 1956.

Presented at the postgraduate course of the American College of Physicians on The Heart—Recent Advances in Diagnosis and Treatment, at the University of Kansas Medical Center, March 21, 1956, under the directorship of E. Grey Dimond, M.D., F.A.C.P. From the Western Reserve University School of Medicine, University Hospitals, and Mount Sinai Hospital, Cleveland, Ohio.

Supported by grants from the United States Public Health Service and the Cleveland

Area Heart Society. Requests for reprints should be addressed to Claude S. Beck, M.D., Lakeside Hospital, 2065 Adelbert Road, Cleveland 6, Ohio.

the accomplished fact. Knowledge must be based upon a large number of observed facts in the research laboratory.

We should learn several lessons from the man who fell over dead. One of these is that the death factor may be small and reversible, comparable to starting or stopping the pendulum of a clock, or turning off and on the ignition switch in a motor. The death factor may also be prevented, as this presentation will show. This experience also opens a new door in cardiology, because this one positive accomplishment implies that there can be more. It is only reasonable to carry out further attempts; and to make these attempts properly, special training in resuscitation will be required by the medical personnel.

We want to make this presentation understandable. We know that, once ideas have become established over a period of years, it is sometimes difficult to change them. These new facts must be understood before they can be accepted, and once they are accepted, then they can be applied to patients. We hope that this orderly sequence of events will take place in reference to this work.

Types of Death in Coronary Artery Disease

There are two types of death in coronary artery disease. One is due to electric currents in the heart which destroy the coördinated mechanism.² The other is due to muscle destruction and failure. Out of every 10 deaths due to coronary disease, a break in mechanism occurs in about eight, and muscle failure occurs in about two. These two types of death are so different that they might appear to be produced by two entirely different types of disease.

THE ELECTRICALLY STABLE HEART

Electrical stability is present when the distribution of oxygen throughout the myocardium is uniform.² Stability does not depend upon the amount of oxygen delivered to the myocardium; a uniformly and deeply cyanotic heart is electrically stable. This statement strikes at the very foundation of the coronary problem. In our many years of research on this problem, red blood to the heart was always considered to be the problem. Our dictum was: "The coronary problem involves red blood to the heart." Now we know that this is not absolutely so. Distribution of blood is more important than absolute quantity. The coronary problem has two facets: (1) distribution, (2) amount of blood available to the heart. Faulty distribution kills 80 to 90% of the victims, inadequate total flow kills 10 to 20% of the victims.

Normally the coronary arteries are capable of carrying at least five times as much blood as the capillary bed receives. Only when the cross-sectional diameter of the large vessels is reduced to less than 25% is there significant

hemodynamic impairment at rest. If distribution is adequate, the occlusive disease in the coronaries may go on to completion before death occurs.

THE ELECTRICALLY UNSTABLE HEART

Electrical instability occurs when the distribution of oxygen is not uniform throughout the heart. We coined the term "oxygen differentials" to describe this condition.² In the laboratory these differentials are produced by ligation of a coronary artery in a pink heart, and by perfusion of red blood into a coronary artery in a cyanotic heart. Contact between blue and pink muscle, or pink and blue muscle, produces these currents. Other factors being constant, the greater the differential the greater the current; the less the differential the less the current. The term threshold of fibrillation may be used to refer to the susceptibility of the heart to develop fibrillation. If the threshold is high, the current produced by the oxygen differential may not be strong enough to be destructive; if it is low, then a small current may be destructive. The following equation may be applied:

Fibrillation index = Current of oxygen differential. Threshold of fibrillation.

When a man while shoveling snow falls over dead in the snow pile, certain factors contribute to this catastrophe. The exercise and the cold "pinked-up" his skin and also his heart. Because of a stenosed or occluded coronary artery, part of the heart could not increase its blood flow enough and thus became relatively blue. The cold air in his lungs may have lowered the fibrillation threshold by cooling the pulmonary venous return to the heart and/or direct cooling of the epicardial surface of the heart. Without the exercise and cold the heart beat would not have been destroyed.

There is no obligate relationship between these currents and death of heart muscle. The production of current and the death of muscle are different biologic processes. Currents can be produced without infarction; infarction can be produced without producing currents strong enough to disturb the coördinated mechanism. The fact that one third of all the victims of coronary artery disease show no infarct, old or recent, attests to this statement. The fact that extensive destruction of heart muscle resulting in failure occurs without producing currents strong enough to fibrillate the heart also attests to the independent nature of fatal currents and muscle destruction. Currents can kill during the process of infarction; they may occur together, but they are independent processes.

How CAN THE HEART BE HELPED

There are two ways in which the crippled coronary circulation can be helped. One is by an even distribution of the blood that enters these arteries. The other is by the addition of blood to that which enters the diseased



Fig. 1.

arteries. One is distribution: the other is augmentation. Distribution is easy to accomplish by operation. Augmentation is not easy. Distribution is accomplished by production of intercoronary channels. Augmentation has several possibilities, none of which appears practical at present. One might open a coronary artery and scrape out the atheroma and calcified plaques, but this is extremely dangerous, and accelerated clotting is likely to occur in such a small artery. A systemic artery might be attached to a coronary artery beyond the stenosed area. This has possibilities, but so far we have had little success in the dog. One can graft a blood supply onto the surface of the heart, but this has been a stubborn problem. In most of the experiments, and we have done many hundreds, it simply does not work. The benefit from a graft is not primarily by blood via the graft. The graft on the heart's surface produces inflammation, and this in turn produces intercoronary channels which produce the benefit. We have had specimens with connections large enough to carry blood between graft and heart in both the dog and the human, but these connections are not the rule. This aspect of the problem needs a great deal more experimentation, because it is possible to find a better method of grafting.

We have tried to convert the coronary sinus into an inlet for blood, and found that red blood delivered into the venous system gave enormous protection to the heart, but the reversed flow lasted for about six weeks and then was replaced by an effective permanent set of intercoronaries which afforded equivalent protection. This operation was difficult to perform and since a set of intercoronaries can be produced more easily, in the last four years we have been using a simpler method.¹

THE PRESENT OPERATION

The present operation is a simple one and consists of four steps. One step is the passage of a ligature around the coronary sinus about 1 or 2 cm. from its ostium in the auricle, constricting the sinus down to a lumen of about 3 mm. This narrowing of the sinus accomplishes certain favorable and unfavorable results. It brings about somewhat greater extraction of oxygen from the venous blood, which normally is already greatly reduced. The mild venous stasis reduces oxygen differentials in the presence of arterial occlusion, and this probably protects the heart with coronary disease. It also produces intercoronary channels. On the other hand, increased capillary pressure may reduce total coronary artery inflow. Our opinion is that this step in the operation makes it more effective. If the sinus is hard to approach at operation, as in cases with cardiac enlargement, this

Fig. 1. Normal dog hearts, with coronary arteries injected, showing intercoronary arterial communications. These vary in normal hearts as they do in normal human hearts. About 9% of the specimens have intercoronary communications, and these are hearts that are protected if occlusive disease should develop. Ninety-one per cent of the normal specimens do not possess these channels.

step is omitted. However, only rarely is this the case. We have seen no ill effects from it at operation.

The second step consists of abrasion of the lining of the parietal pericardium and the epicardial surface of the heart. This produces inflammation, with resultant intercoronary channels. Necrotizing chemicals such as carbolic acid should not be used for this purpose.

The third step consists of the application of about 0.3 gm. of coarsely ground asbestos to the surface of the heart, producing a mild inflammatory reaction. Asbestos is the most effective and least irritating substance that we have tested.

The fourth step is to bring the mediastinal fat into contact with the heart so that it can act as a graft upon the heart. Each step in this operation contributes something to the final result. The operation itself is tolerated remarkably well. It requires approximately one hour to perform. It should be emphasized that there is no need for haste during operation. In no instance has the duration of operation contributed to any untoward complications.

EFFECTIVENESS OF THIS OPERATION

Figure 1 shows normal dog hearts with the coronary arteries injected. Figure 2 shows dog hearts after this operation was done. The presence of intercoronaries is obvious. Figure 3 shows measurements of Mautz-Gregg backflow.⁵ The average backflow in 70 normal dogs is 3.8 c.c. per minute or 228 c.c. per hour. Average backflow in 41 operated dogs is 8.5 c.c. per minute or 510 c.c. per hour. Operation adds an average of 282 c.c. per hour to the circumflex area beyond the occlusion. It is comparable to a transfusion of 282 c.c. of blood added to the quantity already present. This blood is available to meet the crisis of the occlusion. There is no evidence, no scientific measurement, to show that any of the available medical measures add (or subtract) a single drop of blood to ischemic muscle. In dogs undergoing one-step ligation of the descending ramus of the left coronary artery at its origin, the 70% mortality in normal dogs was reduced to 26.6% by operation. This decrease of 43.4% is due to reduction of oxygen differentials by intercoronary channels. The process of infarction was reduced 60 to 70% in size by this operation. These results have been well tested in the laboratory.

LIMITATIONS OF MEDICAL AND SURGICAL TREATMENT

Neither form of treatment cures the disease. Neither reduces the occlusive process in the arteries. Neither prevents further development of arterial disease. Neither restores degenerated myocardium. What operation does accomplish is to make blood available to muscle rendered ischemic by arterial disease. It reduces oxygen differentials; it reduces the currents

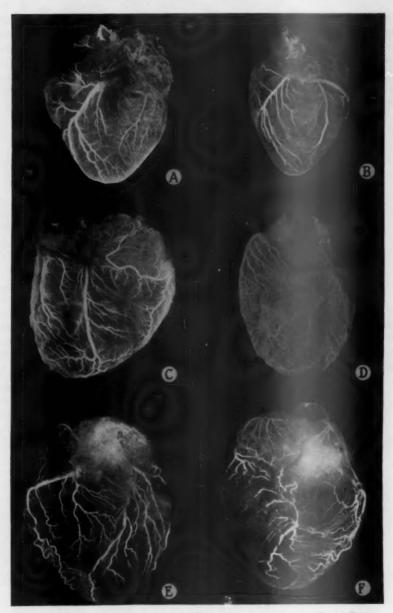


Fig. 2. Hearts after operation. A, B, C and D are dog hearts. E and F are two views of a human specimen. Note the presence of intercoronary arterial communications, especially over the base of the heart.

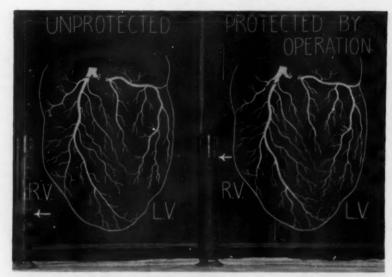


Fig. 3. Average back flow from circumflex artery in normal and operated dog hearts. Operation adds 282 c.c. of arterial blood per hour to ischemic myocardium.

and it saves life. This blood is present to meet the occlusion. The results in humans have substantiated the experimental studies.

It is almost superfluous to state that operation has no relationship to arterial disease. It does not pretend to cure the disease. The point is

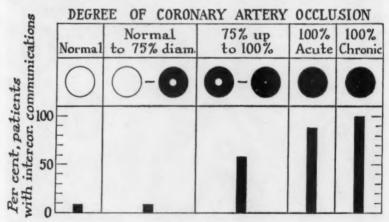


Fig. 4. Presence of intercoronary arterial anastomoses in human hearts, with various degrees of stenosis. Based upon studies by Zoll, Wessler and Schlesinger. Courtesy J. Am. Geriatrics Soc. 4: 322, 1956.

made by some that the disease cannot be produced in animals and, therefore, this work cannot be applied to patients. In answer to this, the statement can be made that coronary arteriosclerosis does not kill the patient. It is the reduction in the lumen of the artery that kills the patient, and the artery can be reduced by a ligature as well as by the disease. Even if it were possible to produce coronary artery disease in dogs, the degree of occlusion and the location of the occlusion could not be controlled with the same precision as the ligature, and as a method for scientific study it would be inferior to the ligature.

INTERCORONARIES PRODUCED BY ARTERIAL DISEASE

This subject has been investigated by Zoll, Wessler and Schlesinger 6 and many others. Their findings are summarized in figure 4. Nine per cent of normal human hearts have intercoronaries; 91% do not have them. These patients were probably born with them. The incidence in dogs is about the same. The incidence does not increase when the narrowing progresses up to 75% of the diameter of the artery. It increases to 58% when the narrowing goes from this degree up to, but not including, occlusion. With occlusion, the incidence is 89% for the acute process and 100% for the chronic process. Our interpretation of this study is that the stenosing process is ineffective in the production of intercoronaries until it becomes severe. Clinical experience attests to the fact that many lives are lost from currents due to oxygen differentials produced by lesser degrees of narrowing. Intercoronaries fail to develop in many of these patients, and the coördinated beat is destroyed. No doubt these channels form more readily in some patients than in others. It would appear that the presence of intercoronaries was necessary to allow the narrowing to become complete and chronic, because they were present whenever chronic occlusion was found. Their presence kept the heart beating so that the narrowing could go on to occlusion and become chronic. The possibility exists that some of the hearts that survived up to chronic occlusion were originally the 9% group born with them. These patients are the ones that are in good position to survive coronary occlusion. They are the ones that the internist regards as excellent recoveries from the disease. They survive the attack because they have intercoronaries. The occlusion makes the intercoronaries develop further, the disease remains static, and the result is excellent. The purpose of operation is to place more people in this favorable group; to take them out of the 91% group and place them in the 9% group.

SELECTION OF PATIENTS FOR OPERATION

1. Prophylactic Group. Up to the present time operation has not been done as a prophylactic measure, but inclusion of this group is under consideration. It is illustrated by a man, age 40 years, who lost his father,

an uncle and two brothers at the age of 41 to 45 years. This man had no symptoms of the disease. The question he put to us was whether he should be protected by the operation now, when the risk of operation was slight and before occlusion developed. Operation was advised.

2. Coronary Insufficiency. Angina Pectoris. Operation is advised

when the diagnosis is made. The risk is small.

3. After One or More Infarcts. The interval between operation and the last infarct should be at least six months. This gives time for repair and for the disease to stabilize so that the condition after operation can be compared to the condition before operation.

CONTRAINDICATIONS

1. Signs of Congestive Heart Failure. These include dyspnea at rest, râles in the lungs, and peripheral edema.

2. Marked Enlargement of the Heart. This indicates extensive myocardial damage, a condition that can scarcely be helped by operation and the risk is definite.

3. Progression of Symptoms. Operation is delayed until the clinical course becomes stabilized. If the stenosing disease is rapidly progressive, operation may transform an impending medical mortality into an evident surgical mortality.

MORTALITY

In the last 48 consecutive patients who were operated upon the mortality was zero. In 170 consecutive patients operated upon since January, 1951, there were two deaths during operation and nine during the early post-operative period, for a total mortality of 6.5%. In 137 patients discharged from the hospital six months to five years, with an average follow-up of two years, the long-term mortality was 13.1%. In a similar series of patients acceptable for sympathectomy in whom operation was not done, the mortality in two years was 30%. These patients were incapacitated enough to consider operation. For comparisons to have value, the two groups of patients must be identical, and it is almost impossible to get identical control groups.

CLINICAL RESULTS

Of 100 patients who were followed six months to five years after operation and who could be evaluated, there was no pain in 40, less pain in 48, and a total of 88% improved. There were 34 better able to work without limitation, and 56 better able to work with moderate limitations, or 90% better able to work. Frequently the patient states that the tightness in the chest is relieved as early as the first week after operation. This improvement is accepted by us because it can be demonstrated that improvement in circulation can be achieved in a few days. In the majority of patients the

degree of improvement is such that only by direct contact with the patient can this be appreciated.

DISCUSSION AND CONCLUSIONS

In recent years the widespread application of operation for coronary disease in many medical centers has been most gratifying. Coöperation between the medical cardiologist and the surgeon is essential. Care must be taken to keep mortality figures as low as possible. Unfortunately, in so doing certain patients will be denied operation even though they could have been helped. Mortality is held against the operation. The greatest amount of good to the largest number of patients will be achieved by a mortality approaching zero. Some internists are quick to ascribe all mortality to the operation and none to the disease. All mortality during and immediately after operation, therefore, is ascribed to operation. Even delayed mortality occurring weeks or months after discharge from the hospital will be ascribed to operation, but we must state emphatically that this should not be so. If the patient goes through the operation and the immediate postoperative period, then the operation cannot kill the patient. Nor can operation make his clinical condition worse. Regardless of what appraisal the clinician places upon the operation, it must be stated emphatically that the operation does not make the patient worse. If the clinical condition deteriorates later on, this is not due to the operation; it is due to the disease. Thus, it is possible to return an incapacitated patient to work for nine months without pain. Then pain returns; he becomes almost disabled again and dies in three months. This result should be considered as good or excellent, because the patient was enabled to return to work without pain for nine months. The operation does not pretend to cure the disease. If the clinician cannot accept this type of thinking, then it is advisable for him not to engage in this development. At the same time, the clinician should recognize that there is no scientific evidence to indicate that medical measures add a single drop of blood to ischemic myocardium. We should recognize this axiom in coronary artery disease: the fate of the patient depends upon the amount of blood available to ischemic myocardium beyond the site of the occluded artery. It now becomes important to decide which is the better way to treat the patient: whether to continue with rest, sedation and other medication, or to have an operation performed. This places responsibility upon the internist. The patient should know that there is an operation for this disease.

The methods for measuring results of operation leave much to be desired. The clinician has difficulty in the appraisal of any patient with coronary disease at any time—death can occur so unexpectedly. We can only accept what the patient tells us: how he feels, how much he is able to do, how much pain he has, what medication he takes, what his wife thinks about his condition on the basis of her observations. We appreciate the

psychologic aspects of coronary artery disease, but it is foolish to state that the improvement after operation is in the patient's mind. The patients themselves reject this idea as nonsense. The majority of the patients were severely incapacitated. They wanted to return to work. They cannot be expected to go through an operation and then say they are better if they are not better. There is no reason for them to falsify this result; indeed, the trend should be in the opposite direction: to expect more benefit than the operation can produce, and this scarcely ever happens. It is a simple matter to demonstrate that operation increases longevity or saves life in the experimental laboratory, but it will be a difficult matter to accumulate comparative data on patients. We are satisfied with the laboratory answer, where all scientific controls have been applied to this problem. The value of this scientific proof is not to be under-rated merely because it was done on dogs and not on humans. It is probably possible to use clinical data that will give an answer in either direction, depending upon the motives of the clinician. We do not expect the question of longevity to be proved to the satisfaction of all clinicians. For the present, the relief of pain and the ability to return to work are sufficient reasons for the patient to accept operation.

ADDENDUM

A series of 100 consecutive patients was operated upon at University Hospitals and at Mount Sinai Hospital, Cleveland, and the operative mortality in this group was 0. One patient had a coronary occlusion before he was discharged from the hospital and this caused his death. This patient was ambulatory, was relieved of his anginal pain and was obtaining a good early result from operation when this occlusion occurred. In each operation the heart was carefully examined and the results of these examinations are given. The left ventricle was enlarged in 40 and normal in 60. An aneurysm was present in 7. There was no observable infarct in 22 and one or more infarcts were found in 78. Arterial disease was observed or palpated in 97 and was not found in 3. The term "salvage" was applied to those in whom the left ventricle was enlarged and in whom there was an area of myocardium with reduced or absent pulsation. Because of severely damaged myocardium the expected benefit from operation in this group was usually considered to be questionable. However, some of the best clinical results were obtained in patients in this category. Indeed, in one patient long standing signs of failure disappeared after operation which was done one year ago. Twenty seven patients were classified as salvage and 73 were classified as good candidates. The common left coronary artery was palpated in each case. It was soft, pulsated and felt to be approximately normal in 76; it was thickened or calcified in 24. The presence or absence of disease in the common left coronary artery is an indication of coronary arterial inflow. If this artery is soft and normal the assumption is made that the inflow of blood is adequate and the problem in physiology and

therapy is that of redistribution in the peripheral areas of myocardium and operation can accomplish a balanced distribution. This record speaks for itself.

SUMMARIO IN INTERLINGUA

In stenosis o occlusion de arteria coronari, le fato del patiente o le fato del can experimental depende de qual quantitate de sanguine in le musculo cardiac esseva previemente apportate per le nunc stenotic o occludite arteria coronari. Iste assertion es valide si le stenosis o occlusion es producite in humanos per morbo arterial e si illo es effectuate in canes per ligatura chirurgic. Un voluminose litteratura medical super morbo de arteria coronari neglige iste veritate axiomatic proque—evidentemente—therapias medical non pote resultar in alterationes del anatomia del arterias coronari. Sed iste anatomia pote esser alterate per medios chirurgic. Le stimulo resultante in tal effectos es un inflammation al superficie del corde producite per agentes mechanic e chimic.

Iste operation produce un distribution uniforme de sanguine in le corde, de maniera que—si e quando un arteria major es occludite—sanguine additional es presente in le musculo ischemic. In casos de occlusion de arteria circumflexe, le operation augmenta le quantitate de sanguine per 282 cm³ per hora. Iste quantitate reduce le mortalitate, le dimension del infarcimento, e anormalitates in le electrocardiogramma, secundo le evidentia de tests comparante le effecto de ligatura de arteria coronari in canes protegite per le operation hic discutite e in canes normal sin ille protection. Post occlusion del branca descendente del arteria sinistro-coronari, le operation protectori reduce le mortalitate per 43% e le dimension del infarcimento per 60 a 70%. Le mesme operation ha essite applicate a patientes con morbo de arteria coronari, e le resultatos esseva lo que nos habeva expectate. Il ha nulle conflicto inter le mesurationes laboratorial e le resultatos clinic.

Le operation deberea esser executate le plus promptemente possibile in le curso del morbo. Le operation non pote arrestar le processo occlusive in le arterias; illo non pote restaurar un degenerate myocardio. Quando extense lesiones muscular rende possibile un dilatation del corde, il es generalmente troppo tarde pro effectuar significative beneficios per le operation. Le operation debe esser retardate usque a al minus quatro menses post un acute infarction myocardial o qualcunque augmento

abrupte in le severitate del symptomas.

Pro le ultime 77 consecutive patientes subjicite a nostre operation le mortalitate esseva zero. Iste excellente resultato esseva obtenite principalmente gratias al caute selection del patientes. Il es probabile que le operation prolonga le vita. In le laboratorio iste assertion es un facto establite. Ab le puncto de vista del symptomas, 90% del patientes evalutate habeva resultatos excellente: 45% es completemente libere de dolor, e le altere 45% ha considerabilemente minus dolores que ante le operation. Similemente, 90% del patientes es hodie economicamente productive: 42% es capabile a travaliar jornatas complete sin ulle restriction, e le altere 48% travalia melio que anteriormente, ben que con certe limitationes.

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CRITICAL ANALYSIS OF PALLIATION PRODUCED BY ADRENALECTOMY IN METASTATIC CANCER OF THE FEMALE BREAST *

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INTRODUCTION

In the absence of any definitive cure, retardation of tumor growth with prolongation of a comfortable and useful life is a worth while achievement in the treatment of patients with metastatic cancer. In women, carcinoma of the breast is one of the most common forms of malignant disease, with a high incidence of generalized dissemination and long-lasting terminal disability. Any means of producing reasonably prolonged and successful palliation is highly gratifying to both patient and physician. It is the more desirable to the latter if it can be ascribed to a specific antitumor effect of the therapy used. There has been increasing evidence that administration or withdrawal of certain steroid hormones may alter the course and clinical manifestations of this type of malignant disease. In 100 cases, with an operative mortality of 5%, Huggins 1 reports remission of varying duration and degree in 38 patients, or 40%. Galante and co-workers found 2,8 evidence of objective improvement in 18 out of 50 cases operated upon. Cade 4,5 reports a series of 56 patients, of whom 40 are evaluated. The operative mortality was 13.6%; excellent results were noted in 27.5%, and satisfactory objective response was obtained in 42.5%. According to this author, 60% of the patients had beneficial results, and in 23% the results were "quite remarkable." Delarue reports a series of 32 cases, with "dramatic objective improvement" in 40.6%. In a series of 38 cases reported by Pearson, adrenalectomy produced objective remission in 45%, and 26.3% of a group of 19 operated upon by Pyrah and co-workers 8 showed a major regression. Hellström observed improvement in 24 out of 51 patients with metastasizing breast cancer after adrenalectomy. In an earlier paper, Taylor et al.10 found evidence of tumor regression following bilateral adrenalectomy in seven out of 16 patients with cancer of the breast. However, the practical importance of this procedure is less the percentage of cases showing objective evidence of tumor regression than

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the total worth of it to the patient, and whether it is associated with improved ambulation and activity as well as a useful and worth while prolongation of life. The purpose of this paper is to evaluate clinically the palliative value and to review the validity of various criteria used in the analysis of results.

METHODS AND MATERIAL.

It has been our feeling that the following requirements should be met if results from adrenalectomy in the treatment of metastatic breast cancer are to be adequately interpreted:

- 1. A sufficient period of time without therapy must be observed to determine the natural course of the disease in the individual case, and to rule out any remission occurring spontaneously, or secondary to withdrawal of other steroid therapy.
- No radiation therapy should be given for a period of at least three months prior to adrenalectomy.
- Adrenalectomy should be delayed until all evidence of regression produced by castration alone has disappeared, and evidence of progression is obvious.
- 4. The post-adrenal ectomy evaluation should be done by the same group of investigators who observed the patient in the period prior to adrenal ectomy.
- 5. The following criteria should be used for:
 - a. Objective response: Regression of all visible or palpable lesions; "bone healing" as indicated by positive radiologic evidence of recalcification of osteolytic lesions, changes in the urinary excretion of calcium and of the serum alkaline phosphatase; regression of pulmonary or pleural lesions, as evidenced by serial roent-genograms.
 - b. Subjective response: Marked and definite relief of bone pain and/ or respiratory symptoms (due to metastatic lesions), and reambulation in those patients who were bedridden or severely invalided because of the malignant disease.

The following results were not considered a worth while response: subjective improvement persisting less than two months without evidence of objective regression; transitory decrease in the urinary excretion of calcium, or recalcification of osseous metastasis with concomitant appearance or progression of other lesions.

Patients with regression of some lesions but without progression of others were considered as "benefited" if there was at the same time definite subjective improvement. In the final evaluation of results, most emphasis was given to the over-all clinical response obtained by the patient if this benefit could be attributed to a specific effect on the metastatic lesions.

Meeting requirements 1 to 3 has been impossible for many of our cases

—in some because of rapid progression of the disease, in others because the separation of two operative procedures, castration and adrenalectomy, has been economically or otherwise unsound and the effects due to each could not be separated.

Fifty-eight female patients with metastatic carcinoma of the breast underwent bilateral adrenalectomy in the Steroid Tumor Clinic of the University of Illinois and the Presbyterian Hospital between February, 1952, and August, 1955. Histologic diagnosis of the primary tumor was available for all cases. Definite evidence of recurrent metastatic disease was obtained for every case, either by biopsy of accessible lesions, cytology of effusions or by analysis of roentgenograms. All but two cases had received previous standard therapy for metastatic disease, and all showed progression of their disease at the time adrenalectomy was performed. The patients were followed at regular three- to five-week intervals and their clinical condition was evaluated.

Serial roentgenograms, chest and bone surveys, serum calcium and alkaline phosphatase and urinary calcium excretion studies were obtained at intervals of four to six weeks and the results correlated with the clinical picture. Most of these studies were done on an out-patient basis. For the urinary calcium excretions the patient was instructed on a low (approximately 150 mg.) calcium diet for the period prior to and during a three-day collection period of urine.

RESULTS

Of the 58 patients who had bilateral adrenalectomy, eight died within the immediate postoperative period; extensive metastatic pleuropulmonary

TABLE 1

	Number Cases	%
Postoperative death	8	16
Not improved	34	68
Worth while palliation	13	26
"Benefited"	3	6
Evaluated	50	
Total	58	_

involvement was the cause of death in five. Two died from hepatic insufficiency secondary to metastatic disease and one from postoperative hemorrhage. In the remaining 50 patients, worth while palliation was obtained in 13, or 26%. Three more patients demonstrated objective regression from the procedure, but worth while palliation did not take place.

CORRELATION BETWEEN VARIOUS FACTORS AND RESPONSE TO ADRENALECTOMY

Since response to adrenalectomy as well as to other hormone therapy remains unpredictable, analysis of various factors assumed to influence the

course of the disease was expected to improve the means of patient selection for such therapy.

1. Age: Usually only patients five years or more past the menopause respond favorably to estrogen therapy. Most reports on results with adrenalectomy fail to show any relationship between age and therapeutic effects after adrenalectomy. In this present series the range of age at the time of adrenalectomy was from 26 to 66; the age distribution and response can be seen in table 2. Our data are pooled with those given by Huggins, Cade, Galante and Pearson, and are shown in table 2.

It would appear from these combined data that the better results can be expected in the 40-to-50 age group.

2. Correlation of Response to Adrenalectomy with Duration of Clinical Cancer-free Period: It is assumed that this period indicates the degree of

TABLE 2 Number of Cases

Age	Huggins	Cade	Galante	Pearson	Ours	Total
Under 40 40-50 50-60 60-70+	13 42 31 9	8 15 7 1	9 15 16 5	1 9 2	14 11 18 7	45 92 74 22
Total	95	31	45	12	50	233

Improved

			1	1 . 1		1	1
Age	Huggins	Cade	Galante	Pearson	Ours	Total	%
Under 40 40–50 50–60 60–70+	3 19 12 4	1 8 3 0	4 4 7 1	0 4 1	3 4 5 1	11 39 28 6	24.4 42.3 37.8 27.2
Total	38	12	16	5	13	84	36

malignancy of the tumor. However, the rapidity of growth and spread of a tumor depends not only upon the yet ill-defined degree of malignancy but also on host-resistance factors which are equally unknown. Huggins ¹ has shown that better results can be expected in those patients who had a prolonged interval between mastectomy and onset of clinically demonstrable recurrent or metastatic disease. Table 3 compares our data with those given by Huggins.

3. Histology of the Primary Tumor and Response to Adrenalectomy: Survival and response to specific therapy have been reported to be influenced by the histologic grade and type of the primary tumor. According to Huggins, the tumors most responsive to adrenalectomy are those composed of spheroidal cells with acini having lumina whose lining is one cell in thickness. However, mammary tumors are seldom monomorphous, and classi-

TABLE 3

Time Number Case		r Cases	Improved		%		Total	Improved	%
Mastectomy- Recurrence	Huggins	Taylor	Huggins	Taylor	Н.	T.	Cases	Cases	
Less than 1 year 1-2 years 2-5 years	28 29 30	11 10 10	3 14 16	2 5 3	10.7 48.2 53.2 62.5	18.1 50.0 30.0 40.0	39 39 40 13	5 19 19	12.8 48.7 47.5 53.8

fication of these tumors is difficult because of the wide spectrum of structural variation seen in a single lesion.

We have been unable, in retrospect, to find any correlation between the histologic type of the primary tumor and the response to therapy in our group of 58 patients, nor could any distinctive morphologic pattern be found on the slides of those who responded favorably.

4. Menstrual Age of Patients: It has been shown repeatedly by both urinary estrogen and endometrial biopsy studies that cessation of menstrual periods is not equivalent with cessation of estrogen production either by the ovaries or other extragonadal sources. Huggins 'states that patients with higher estrogen titers in the urine respond better than those who excrete only small amounts. Urinary estrogen determinations were not done in this group of patients. We have separated our patients into two groups, premenopausal and postmenopausal, and have compared the response to adrenal ectomy accordingly. The findings are summarized in table 4. In an attempt to determine whether adrenal ectomy alone might produce any regression in menstruants, two patients had the operation without preceding oophorectomy. One, 33 years old, failed to show any subjective or objective improvement following adrenal ectomy, and bilateral oophorectomy was performed two months later, without subsequent regression. The other patient, 49 years old, with extensive and generalized osteolytic metastasis,

TABLE 4

	Premeno	pausal Group	Postmenopausal Group		
	Number of Cases	Regression after Adrenalectomy	Number of Cases	Regression after Adrenalectomy	
Adrenalectomy alone	2	0	14	5	
Combined adrenalectomy and oophorectomy	5	2	6	0	
X-ray castration before adrenal- ectomy	7	4	_	-	
Oophorectomy before adrenalec- tomy	8	2	6	0	
Oophorectomy before onset of disease	-	Garinga	2	0	
Total .	22	8	28	5	

failed to show any objective evidence of remineralization, and three and one-half months later surgical castration was performed. Recalcification

of osteolytic lesions appeared one month later.

5. Previous Response to Therapy: As most of the patients in this series had had other steroidal therapy prior to adrenalectomy, it was of interest to see whether there was any correlation between the results obtained with adrenalectomy and those of other endocrine management. Pearson et al. 11, 18 suggested that those who fail to respond to castration will also fail to respond to adrenalectomy, whereas such correlation was found to be valueless by Cade. In order to evaluate critically the effects of different therapeutic regimen, sufficient time-i.e., at least two to three months-has to separate each one. Adhering to these criteria, we have been unable to secure any accurate estimation as to the selection of cases for adrenalectomy based on the response to previous therapy. Of 28 patients treated with androgens prior to adrenalectomy, eight experienced gratifying relief with this management, but only four of these showed another remission following adrenalectomy. Of the 20 cases uninfluenced by androgen therapy, three had a worth while beneficial result after adrenalectomy. Seven patients had estrogen treatment, to which only one responded favorably, but none showed any response to adrenalectomy. Seven patients could be evaluated as to the separate effects of castration and adrenalectomy. Four were failures to both procedures, whereas only one out of two who had shown regression after castration did so after adrenalectomy. One patient had a clinically and objectively worth while palliation following adrenalectomy after she had failed to benefit from castration.

6. Urinary Calcium Excretion: Urinary calcium excretion studies in patients with osseous metastases have been advocated by Laszlo, ¹² Pearson et al. ¹³ and Emerson ¹⁴ as a useful tool in the selection and evaluation of therapeutic effects in these patients. Urinary calcium excretion on an outpatient basis was obtained in 17 patients with known osteolytic metastasis, and the results were correlated with the subsequent clinical course. It is understood that these studies on ambulatory patients lack the precision of those obtained on metabolic wards, the purpose being to evaluate the validity of a relatively simple test for out-patient follow-up. Collections were obtained prior to adrenalectomy, and at three- to four-week intervals thereafter. At the same time, blood was obtained for determinations of serum calcium and alkaline phosphatase.

Only 10 of 16 patients with roentgenologically proved osteolytic metastasis had an elevated (higher than 150 mg./24 hrs.) urinary calcium prior to adrenalectomy. A significant drop in calciuria occurred in six patients after operation, coinciding with clinical improvement in only three, whereas the remaining three failed to show any clinical or roentgenologic evidence of regression despite improvement of urinary calcium excretion. Eight patients showed a rising calciuria, correlating with progressive disease in

six, while two others had both subjective and radiologic evidence of remission not indicated by the urinary findings. Two further patients, in spite of proved osseous metastasis, had a normal calciuria.

Correlation of clinical and radiologic findings with urinary excretion of calcium during the later postadrenalectomy course was found to occur in only nine of 17 cases.

Decrease in the urinary calcium excretion, with relief of bone pain in the postadrenalectomy period, was found in several patients and lasted up to two months, but was never concomitant with or followed by radiologic evidence of recalcification. In other instances, three to six months after adrenalectomy, while roentgenograms showed healing of bone lesions, the increase in urinary calcium excretion indicated progression of the destructive process in bones. In 10 out of 15 patients a phosphatase flare was observed in the immediate postadrenalectomy period. This coincided with clinical improvement in four.

DISCUSSION AND COMMENT

Critical analysis of adrenalectomy-induced regressions in patients with metastatic cancer of the breast, reported by this group and others, raises many doubts as to the actual efficiency and real worth of the procedure. This is due, at least partially, to different criteria used by various observers. Despite some undeniably remarkable but as yet unexplained results, any unprejudiced observer remains more impressed by the (still) unsatisfactory methods of patient selection, the frequently observed dissociation between clinical course, and various objective changes.

We have been unsuccessful in improving possible means of predicting which patients are likely to respond to adrenalectomy. There are conflicting statements in the literature regarding the rôle of age in prognosis and survival of patients with breast cancer. It is questionable whether the apparent better response in the 40-to-60 age group has any real significance. Correlation between menstrual age and response to adrenalectomy could not be demonstrated by our group. Similarly, no accurate estimation of prognosis could be obtained by comparing results of previous therapy with those seen after adrenalectomy. The impression is held by some 15 that patients who benefit from castration are most likely to have another remission following adrenalectomy. Perhaps a better correlation of these factors may be obtained by an analysis of a large number of pooled cases, such as is being prepared by the Subcommittee of Steroids in Breast Cancer of the American Medical Association. If the rationale that adrenalectomy acts by removing an extragonadal source of estrogens is adhered to, it would seem more logical to remove all such sources at once, rather than to have "estrogendependent" tumor tissue spread and create irreparable damage. However, this contention was not proved by better results in cases where both adrenalectomy and oophorectomy were performed simultaneously. Dissociations

between clinical response and that evidenced by laboratory or radiologic data, and even between various objective criteria, have been repeatedly observed. Obviously no single clinical or laboratory criterion can be used as a standard against which tumor regression or progression can be assessed. The validity of critical evaluation must depend on the degree of agreement of almost all criteria as a whole, as well as the total benefit obtained for the patient.

Bone pain which is present in most patients with osseous metastases is widely used as a clinical criterion of the effectiveness of the therapeutic palliation. It is well to remember, in analyzing results, that in addition to a varying psychologic component there are different mechanisms underlying the origin of this type of pain. Increased medullary pressure due to increased cellularity was shown by Petrakis ¹⁶ to produce bone pain; the same would be true of changes due to secondary noninfectious inflammatory changes. On the other hand, the pain can be produced by actual nerve root compression, and some patients of the older age group may have actual arthritic pain. Therefore, it is not surprising to observe pain relief without other evidence of tumor regression or bone healing, either by roentgenograms or by biochemical alterations in serum or urine.

Osseous metastases in mammary carcinoma are predominantly osteolytic, but a lesion may not be demonstrable until 40% of the bone has been destroyed. The radiologic manifestations of remineralization of osteolytic lesions are a poorly understood phenomenon, and Hallberg et al. 17 feel that they are actually of little value as an objective criterion. The character of a lesion at a given time depends on the destructive action of the metastatic tumor and the reparative reaction of the injured bone. Any increase in density in an originally lytic lesion is likely to be interpreted as evidence of healing, but cases are frequently seen in which a metastatic area in bone increases in size and density simultaneously. With the lack of concomitant histologic studies, it remains a debatable question whether the observed changes represent osteoblastic progression or true healing. Noninfectious inflammatory changes occur as a reaction to carcinomatous deposits in bone, and several earlier observers held the belief that these reactive processes were responsible for either the spontaneous regression or the formation of new bone. Finally, the radiographic density of metastatic areas in bones depends also on variable technical factors in the roentgenogram which may be of importance in interpreting serial films.

Metastases to bones are reflected biochemically by changes in the metabolism of calcium, and urinary calcium excretion studies ¹⁸ are used as an objective criterion for the evaluation of results in patients with osseous lesions. These studies are based on the postulation that, in normal persons on a low calcium intake, the urinary calcium ranges from 50 to 150 mg./24 hrs., and that active osteolytic metastasis will cause an excess of about 100 mg./day for every gram of bone destroyed. It is known ^{18, 19, 20, 21} that

many factors influence the renal excretion of calcium, and that calciuria may be very variable, even if the intake is kept constant. Sex and cortical steroids are known to influence the urinary excretion of calcium in patients without malignant bone disease. The effects of adrenalectomy on calcium excretion on such patients are not known. Using such studies as an index of tumor regression and in the presence of steroid therapy may well produce an erroneous interpretation.

The incidence of osseous metastasis in breast cancer is from 50 to 75%, 22, 23 and varying degrees of hypercalcemia are found in 9 to 18% of these cases. 24, 25, 26 The process of bone destruction (of which elevation of serum calcium is one biochemical manifestation) and of reparative activity varies greatly from one patient to another and from time to time in the same patient. Even in patients without bone disease, variations as great as 1.8 mg. in either direction have been found. If, following therapy, previously elevated serum calcium values return to normal, it is presumed that excessive osteolysis of bone was inhibited. Such conclusions should, however, be drawn only if other objective evidence of tumor inhibition is obtained simultaneously. In some instances the decrease in serum calcium may result from a direct effect of the therapy on calcium metabolism.

Changes in activity of the serum alkaline phosphatase are assumed to reflect manifestations of altered hepatic and osseous functions. The distinction between these two factors, supposed to be readily made with the help of other liver function tests, is necessary in the evaluation of therapeutic results. The so-called phosphatase "flare" after adrenalectomy or other therapeutic measures is interpreted as evidence of bone repair. However, differentiation between attempts at bone regeneration and change to osteoblastic metastasis which also causes an increase in the activity of this enzyme can well be impossible. It has been shown that elevation of serum alkaline phosphatase may be the only liver function test of significance in detecting early hepatic metastasis, and subclinical liver dysfunction sufficient to cause minor failure of excretion of the enzyme is fairly common in patients whose general health has been impaired by disseminated cancer. It is conceivable that this dysfunction may be further increased after major surgery, and the elevation of alkaline phosphatase not be indicative of tumor regression in bone at all.

In the analysis of serial chest films, other pathologic conditions, such as perifocal exudative changes, pneumonitis or atelectasis, may be interpreted as neoplastic lesions and their clearing wrongly attributed to a regression of carcinomatous metastasis.

Gross shrinkage of soft tissue metastases, lymph nodes and reëpithelization are often dramatic results and are taken as convincing evidence of the efficiency of therapy. But, although they are uncommon and unsupported by good control studies, spontaneous regressions are known to occur, and it is possible that the observed changes are due to inhibition of secondary

inflammatory changes or to effects on the stromal component of the lesion. Other factors, such as secondary infection or delayed healing, are of some importance in the pathogenesis of rampant ulcerative lesions and have to be considered in analyzing results with adrenalectomy.

Conclusion

1. Adrenalectomy produced worth while palliation in patients with metastatic cancer of the breast in only about 25% of our cases.

2. No correlation could be demonstrated between previous response to various therapies and the results following adrenalectomy.

3. The evaluation of objective regression of metastatic breast tumor is difficult, and conclusions may be fraught with errors.

4. Further evaluation of a large pooled series of cases is necessary before the validity of the procedure can be established.

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SUMMARIO IN INTERLINGUA

Le analyse critic del resultatos de adrenalectomia in patientes con metastatic carcinoma de mamma subleva multe dubitas in re le ver valor de iste procedura. Le importantia practic de adrenalectomia in patientes con metastatic carcinoma de mamma deberea esser determinate secundo le criterio de regressiones significative que rende le patiente capace a viver un relativemente normal e confortabile vita durante un appreciabile periodo de tempore e non simplemente secundo le criterio del procentage de casos exhibiente un regression transitori o partial del tumor.

In un serie de 58 patientes feminin con metastatic carcinoma de mamma, 26% manifestava formas significative de regression in consequentia de adrenalectomia bilateral, durante que un total de 34% monstrava regressiones objective con o sin palliation de importantia practic. Le valor de 26% es plus basse que le valores generalmente trovate in le litteratura. Iste facto reflecte possibilemente al minus in parte le differentias inter le criterios usate per le varie observatores.

Nulle accurate estimation del valor prognostic de adrenalectomia esseva obtenibile in iste studio per correlationar le sequente factores con le resultatos del therapia: (1) Etate menstrual e chronologic del patiente al tempore del operation; (2) resultatos de un previe therapia hormonal; (3) duration del periodo non-canceric post le mastectomia initial; e (4) typo histologic del tumor. Tamen, il es possibile que un plus extense serie de casos revelarea tendentias de signification statistic le quales non es apparente in le plus restringite serie del presente reporto.

In general, adrenalectomia esseva executate in feminas premenopausal post o insimul con oophorectomia. Regressiones esseva notate in feminas postmenopausal con e sin previe o simultanee oophorectomia. Duo feminas premenopausal in qui adrenalectomia esseva executate ante le tempore del oophorectomia non manifestava ulle signo de regression como effecto del adrenalectomia. Un de iste patientes experientiava un multo remarcabile regression quando oophorectomia esseva executate circa tres menses plus tarde.

Ben que alterationes del metabolismo e del excretion de calcium e etiam variationes in le phosphatase alcalin del sero es frequentemente considerate como prova de regression, nos signala que il existe multe observate casos de dissociation inter le responsa clinic e iste constatationes. Assi nos recommenda le requirimento de un complete accordo del studios biochimic, del curso clinic, e del studios radiologic como criterio del occurrentia de regression in patientes con metastatic carcinoma de mamma.

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STREPTOCOCCAL BACTEREMIA WITHOUT EN-DOCARDITIS: CLINICAL OBSERVATIONS *

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Rosenow and Brown 1 described 144 cases of bacteremia due to a variety of organisms encountered at the Mayo Clinic during the three years from 1934 through 1936. Herrell and Brown 2 in 1941 compared the results of treatment of bacteremia at the Mayo Clinic before and after the advent of the sulfonamide compounds. The treatment and results in cases of subacute bacterial endocarditis due to penicillin-sensitive streptococci and to enterococci have been described by Geraci and one of us (Martin). 3, 4 Experiences in the treatment of 137 patients with bacteremia due to gramnegative bacilli at the clinic in a 15-year period also have been reported. Because of the continued interest of our group in such infections, it was thought pertinent to review our experiences with streptococcal bacteremia without evidence of endocarditis.

It is the purpose of this paper to present 34 cases of streptococcal bacteremia without endocarditis encountered at the Mayo Clinic during the 15year period, January 1, 1940, through December 31, 1954. We included only cases in which the clinical picture was unequivocally consistent with the diagnosis of bacteremia and in which two or more positive blood cultures were obtained. No cases in which there was clinical or anatomic evidence of valvular disease were included. Victims of so-called transient bacteremia. such as one encounters in patients who have just undergone dental instrumentation and in whom bacterial invasion of the blood stream is fleeting, were not included.

The bacteriologic studies in connection with these cases were carried out in the Section of Bacteriology.

CAUSATIVE ORGANISMS

Streptococcus pyogenes was the offending agent in 15 cases, S. mitis in eight, and S. faecalis in 11. In six of the last patients, other organisms were found along with the S. faecalis. In five cases these other organisms were gram-negative bacilli, and in one, Micrococcus pyogenes. The gramnegative bacilli were Escherichia coli in two cases and Proteus vulgaris in three.

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AGE AND SEX

The ages of the patients ranged from two days to 80 years (table 1). Although no age group was immune, the age groups from 40 through 79 years were represented by the largest number of patients. The age groups 20 through 39 years were least represented.

Twenty-two of the patients were males and 12 were females.

TABLE 1
Age and Sex of Patients and Causative Organisms

Streptococci	Sex	Age, years									Total
os epicoces	July	0-9	-9 10-19	9 20-29	30-39	40-49	50-59	60-69	70-79	80-89	
S. pyogenes	M F	1	2 2			2	1 2	1		1	8 7
S. mitis	M F	1	1		1	1 1	1	1	1		7
S. faecalis	M F	1		1	1			1	1		3 2
S. faecalis and associated or- ganisms	M F					1	1	1 1	2		4 2
Total		4	5	1	2	6	5	6	4	1	34

Underlying Illness or Preceding Surgical Procedure

The underlying illness or preceding operation, or both, of each patient are given in tables 2 and 3. In 10 of the 15 patients with bacteremia due to *S. pyogenes* there were evidences of suppurative conditions elsewhere in the body. It is difficult to state with exactitude in each case whether the suppurative conditions precipitated or complicated the bacteremia. Of the 15 patients, two who had pyelonephritis had undergone urologic manipulation. Of the remaining patients, two had otitis media with mastoiditis, two had streptococcal pharyngitis, two had osteomyelitis (one of whom also had diabetes mellitus), one had erysipelas, one cirrhosis, one pneumonia with a bronchopulmonary fistula, and one acute porphyria. In three patients no underlying illness was recognized.

Suppurative polyarthritis was noted in two cases of bacteremia due to *S. pyogenes* (one patient also had suppurative ophthalmitis), mycotic aneurysm in one and acute hemorrhagic nephritis in two; these appeared to be definite complications of the bacteremia. Such complications were noted only in the patients whose bacteremia was due to *S. pyogenes*.

Of the eight patients whose bacteremia was due to *S. mitis*, two had undergone surgical procedures. One had had a mastectomy and the other a transurethral resection. Two of the eight patients had diabetes. One

TABLE 2
Underlying Illness Preceding Bacteremia, Exclusive of Those
Considered to Be Complications

			S. faecalis			
Illness	S. pyogenes	S. milis	Alone	With other		
Otitis media and mastoiditis Pharyngitis Osteomyelitis	2 2 1	3				
Erysipelas Diabetes Pneumonia Porphyria	1 1* 1	2				
Cirrhosis Pyelonephritis Omphalitis and peritonitis Pyelophlebitis and peritonitis Acute nonspecific gastroenteritis Carcinoma of colon	1 2	1 1	1	1		
Biliary stricture None detected	3	1	4	1 4		
Total	15	8	5	6		

^{*} Also had osteomyelitis.

of these was the patient who had undergone transurethral resection. One infant had omphalitis and peritonitis. Another patient had pyelophlebitis and peritonitis. Three patients having bacteremia due to *S. mitis* had had preceding sore throats.

Ten of the 11 patients whose bacteremia was due to *S. faecalis*, either alone or associated with other organisms, stand in sharp contrast to the remaining patients of the series in that the apparent portals of entry were gastrointestinal or genitourinary. This finding is reminiscent of the data that we have accumulated on bacteremias owing to gram-negative organisms.⁵ Of the six patients whose infection may have arisen via the geni-

TABLE 3
Operation Preceding Bacteremia

Operation			S. faecalis		
	S. pyogenes	S. milis	Alone	With other organisms	
Transurethral resection Cystoscopy Gastric resection	2	1	2	1 2 1	
Mastectomy Dental extraction Hysterectomy	1	1	1		
None performed	12	6	î	2	
Total	15	8	5	6	

tourinary tract, five had undergone transurethral resection or manipulation, and one had had a penetrating hydatid mole necessitating hysterectomy. Of the four patients whose gastrointestinal tracts appeared to be a likely portal of entry, one each had had acute gastroenteritis, biliary stricture, gastric resection and carcinoma of the colon. The remaining patient in this group had recently undergone dental extraction.

CLINICAL AND LABORATORY FINDINGS

Some of the more important clinical and laboratory findings in the cases of bacteremia are recorded in table 4. Fever was noted in all patients except two who were in shock. One was the infant two days old who had omphalitis and peritonitis and a subnormal temperature. The second patient was in shock, ostensibly as a consequence of generalized peritonitis; necropsy disclosed gangrenous appendicitis and suppurative pyelophlebitis.

TABLE 4
Selected Clinical and Laboratory Findings

Findings	Cases
Fever (more than 100.3° F.)	32
Chills	26
Disturbances of sensorium	6
Profuse sweating	6 3 2 2 6 3 3
Severe headache	2
Shock	2
Lymphadenopathy	6
Meningismus	3
Splenomegaly	3
Anemia*	25
Leukocytosis†	24
Albuminuria	23
Hematuria (microscopic)	19

* Less than 12 gm. of hemoglobin in males; less than 11 gm. of hemoglobin in females. † More than 10,000 per cubic millimeter.

Temperatures ranged from 100.3° to 107° F. and were usually of a spiking nature. Chills were described by 26 patients. All patients showed some degree of malaise. Vomiting and stupor occurred in some cases. The pulse rate was usually elevated in proportion to the fever. In an occasional case of bacteremia a soft systolic precordial murmur was heard initially, raising the question of endocarditis. No case was retained in the series wherein the question of endocarditis persisted.

Twenty-five patients were considered to be anemic. Leukocytosis was present in 24 cases; in one patient who had recently received roentgen therapy the leukocyte counts were less than 5,000 cells per cubic millimeter. The sedimentation rate (Westergren method) was in excess of 30 mm. in one hour in 14 of the 15 cases in which it was determined. Abnormalities found on urinalyses in some instances undoubtedly reflected an underlying urologic disease rather than a nephrotoxic effect of the bacteremia.

TREATMENT AND RESULTS

All 15 patients who had bacteremia due to *S. pyogenes* received treatment. For the eight who were treated prior to 1945, supportive measures, surgical attention, when required, and sulfonamides were employed. Four of these eight patients died and four recovered. Of those who recovered, two were children with otitis media and mastoiditis. Of the two adults who recovered, the one with erysipelas of the face received sulfonamides and roentgen therapy, and the other with bronchopulmonary fistula and empyema following pneumonia received sulfonamides and underwent surgical drainage. Of the four in this group who died prior to 1945, one had cirrhosis of the liver, one bilateral pyelonephritis, one fulminating suppurative polyarthritis, and one diabetes mellitus with osteomyelitis of the vertebrae.

Of the patients with bacteremia due to *S. pyogenes* seen after penicillin became generally available, four recovered and three died. Two of the latter were treated in 1945 with what we would consider, retrospectively, suboptimal doses of penicillin. The third death occurred in the patient with a fulminating and severe infection which was complicated by such

phenomena as suppurative polyarthritis and panophthalmitis.

Of the eight patients whose bacteremia was due to *S. mitis*, two were treated with sulfonamides in the pre-penicillin era; one of these recovered and the other died. Only one of the six patients with this condition encountered after 1945 died. This patient was the infant with omphalitis and peritonitis who had received a solitary dose of a tetracycline compound by the intramuscular route just before death; the other five patients received penicillin.

All patients with bacteremia due to *S. faecalis* alone were seen after 1945. Four patients received penicillin and recovered; the fifth patient was dismissed from the hospital after cultures of the blood became negative, but death occurred 10 days later at home. This fifth patient was 80 years old and a victim of carcinoma of the prostate. He had received one of the tetracycline group of compounds, which members of our group do not now consider the treatment of choice. Two patients with bacteremia due to *S. faecalis* associated with other organisms were treated with sulfonamides prior to 1945, and both died. Of the four patients with this combination of conditions treated with penicillin and other antibiotics after 1945, one patient died. He had a large subdiaphragmatic abscess following gastric resection for carcinoma.

We have pointed out in the past that bacteremias due to proteus are not benign. Two of the three patients in this group who died had bacteremia due to S. faecalis in association with proteus. The patient whose bacteremia was due to S. faecalis in association with M. pyogenes also died, but the two patients with bacteremia due to E. coli in addition to the S. faecalis recovered.

Study of the associated conditions in the 13 fatal cases indicates that the deaths were in patients with serious associated conditions, and in many

instances the associated condition itself was incurable and responsible for the death (table 5).

COMMENT

Rosenow and Brown,¹ in their review of cases of bacteremia covering a three-year period, found the bacteremia in 61 of 144 cases to be due to hemolytic streptococci. We have encountered only 34 patients with bacteremia due to all types of streptococci. Therefore, the incidence of streptococcal bacteremia encountered at this clinic apparently has decreased from more than 20 cases annually to slightly more than two since the advent of chemotherapy and antibiotics.

The mechanism involved in the decreased incidence of streptococcal bacteremia may concern the action of antibacterial agents in eliminating the infectious precipitants of that condition. Employment of the agents for patients with such conditions as otitis media and streptococcal pharyngitis, as well as their judicious administration for patients who have recently

TABLE 5

		A ALDED C
	Condit	ions Associated With Fatal Bacteremia
Organism	Deaths	Associated Conditions
S. pyogenes	7	Bilateral pyelonephritis, 2 cases; suppurative polyarthritis, 2 cases; cirrhosis, mycotic aneurysm, abdominal aorta, acute porphyria, and diabetes mellitus with osteomyelitis of spinal column
S. mitis	. 2	Suppurative pyelophlebitis and peritonitis following gangrenous appendicitis, $1\ \mathrm{case}$; omphalitis and peritonitis, $1\ \mathrm{case}$
S. faecalis only	1	Carcinoma of prostate
With other organisms	3	Carcinoma of colon, 1 case; carcinoma of urinary bladder,

undergone surgical treatment and who have streptococcal infections, appears to hinder the bacteria from invading the blood stream.

The previous studies by Geraci and one of us (Martin) disclosed 21 patients suffering from subacute bacterial endocarditis due to *S. mitis* given antibiotic therapy at the clinic in 25 months from January, 1951, through January, 1953,⁸ and 33 patients with enterococcal endocarditis seen from January, 1944, through December, 1953.⁴ It is obvious, then, that today streptococcal endocarditis is encountered considerably more frequently at this clinic than is streptococcal bacteremia without endocarditis.

Of 137 patients with bacteremia due to gram-negative bacteria studied previously, ⁵ 14 had diabetes mellitus and four had severe liver disease. In the present series of 34 patients, three had diabetes and one had cirrhosis. Because recent dental extraction may be important in the genesis of streptococcal endocarditis, attention is called to the two patients in our series who had recently had teeth pulled. It has been suggested that the stress of surgical operations, with resultant phenomena including the probable release of large amounts of adrenal steroids, may increase the patient's sus-

ceptibility to such complications as bacteremia. In our series, 15 of the 34 patients had had surgical procedures, including urologic manipulations.

Of the 34 patients treated in this series, 13 died; however, all had serious associated illnesses. Furthermore, the majority of deaths occurred among those patients who had received only sulfonamides. The mortality rate was more acceptable after the advent of penicillin. Twelve patients received sulfonamides and seven died. Twenty patients received penicillin and five died; of the five, two patients were treated before 1946 and received inadequate amounts of penicillin, and three had serious underlying diseases, which probably made recovery virtually impossible. Two patients who died had received one of the tetracycline group of compounds; the amount of the agent that one of these patients received was inadequate.

PRESENT METHODS OF TREATMENT

In treating bacteremias due to S. pyogenes, we have found that 1,000,000 units of procaine penicillin G given intramuscularly every 12 hours produces satisfactory results. We are attempting at present to utilize the probable synergistic effect of combined treatment with a penicillin compound and a streptomycin compound in bacteremia due to S. mitis and S. faecalis. In the studies on streptococcal endocarditis s, it was apparent that combinations of penicillin and streptomycin often have increased bactericidal effects when compared to penicillin alone. The attempting to combat bacteremia due to S. mitis, we have found that 1 gm. of streptomycin and 1,000,000 units of procaine penicillin G given intramuscularly every 12 hours yield satisfactory results. In such treatment, dihydrostreptomycin may be substituted for streptomycin, or equal parts of each may be used.

Since most strains of *S. faecalis* are more resistant to penicillin than are the other strains of streptococci, we use at least 6,000,000 units of penicillin G intramuscularly or intravenously, together with 2 gm. of streptomycin

daily, when attempting to eradicate that organism.

When the individual patient requires more than 6,000,000 units of penicillin daily, we usually resort to continuous drip through a polyethylene catheter inserted into a vein in the arm. In such cases we are in the habit of dividing the total daily dose of aqueous crystalline penicillin G into equal parts, and placing half of the amount in a liter of saline solution and the other half in a liter of 5% glucose in distilled water. To each liter of solution we also add 25 mg. of heparin in an attempt to decrease the incidence of chemical phlebitis. The apparatus for administering the solutions can usually be adjusted so that 24 hours are consumed in giving the 2 L.

If doubt arises as to the merit of the regimen being used in an individual case of enterococcal bacteremia the so-called serum bactericidal test may be used. In this test the patient's serum containing the given antibiotics is pitted against the organism isolated from the patient's blood stream.

If the patient's serum under these circumstances, when diluted 1 to 4, does not produce a bactericidal effect on the organism, we increase the dose of penicillin until such an effect is produced.

Treatment is continued until three successive negative blood cultures have been obtained, and the patient remains afebrile for at least five days. There is little danger of toxic effects from the use of streptomycin in the amount mentioned in the presence of normal renal function if treatment does not exceed two weeks.

If the bacteremias due to *S. faecalis* are associated with gram-negative organisms, we initiate antibiotic therapy empirically with one of the tetracycline group of compounds in addition to penicillin and streptomycin, on receipt of report of the blood cultures. If in vitro inhibition tests later indicate that the choice of treatment is a poor one, one can reëvaluate the program. However, if the patient appears to be improving on a given regimen, we do not alter it merely because the so-called sensitivity tests would indicate selection of another agent.

We are currently investigating the feasibility of giving penicillin V^s by the oral route, in place of penicillin G given intramuscularly, to patients with bacteremia due to organisms highly sensitive to penicillin, such as S. pyogenes and S. mitis. Tentatively at least, we give double the usual amount of the agent when relying on penicillin V and administer it in four equally divided doses throughout the day.

SUMMARY

Thirty-four cases of streptococcal bacteremia without endocarditis encountered at the Mayo Clinic over a 15-year period have been reviewed. In this series *S. pyogenes* was the most common streptococcal organism to invade the blood stream. The frequency of streptococcal bacteremia has decreased and the prognosis is good for patients with streptococcal bacteremia without serious underlying disease if adequate amounts of penicillin alone, or penicillin in combination with streptomycin, are given.

SUMMARIO IN INTERLINGUA

Esseva revidite 34 casos de bacteremia streptococcal sin endocarditis incontrate al Clinica Mayo in le curso de un periodo de 15 annos.

Streptococcus pyogenes esseva le agente responsabile in 15 casos, Str. mitis in octo, Str. faecalis in 11. In sex del patientes de iste ultime gruppo, altere organismos esseva trovate insimul con Str. faecalis. In cinque casos iste altere organismos esseva bacillos Gram-negative; in un caso illos esseva Micrococcus pyogenes. Le bacillos Gram-negative esseva Escherichia coli in duo casos e Proteus vulgaris in tres.

Le morbo subjacente e su complicationes in iste 34 casos septicemic es presentate, e le moderne routine de tractamento es discutite.

Le frequentia de bacteremia streptococcal ha decrescite. Le prognose pro patientes con bacteremia streptococcal sin serie morbos subjacente es bon si adequate quantitates de penicillina sol o de penicillina in combination con streptomycina es administrate.

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KLEBSIELLA IN RESPIRATORY DISEASE *

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INTRODUCTION

DURING the last quarter of a century, considerable investigation has revealed the necessity for revising the classification of tribes of bacteria belonging to the family Enterobacteriaceae. Falling into this category is the tribe Escherichiae which, in Bergey's Manual, consists of three genera: Escherichia, Aerobacter and Klebsiella. Among clinicians, it is a common impression that Klebsiella pneumoniae and Aerobacter aerogenes are two distinct and separate organisms, the former being associated with respiratory infections, the latter with abdominal and urinary infections. impression is no longer tenable. Extensive studies by Kauffmann,2 in Scandinavia, and Edwards,8 in this country, have indicated the lack of unequivocal morphologic, biochemical and serologic criteria which could serve to distinguish Klebsiella from Aerobacter. Consequently, it has been recommended that both organisms be included in a single genus which, from the standpoint of priority, should be called Klebsiella, and that individual strains within the group, distinguishable by differences in capsular antigens, be differentiated through the use of Arabic numerals. recommendation was adopted in our laboratory in 1952, and since then we have been attempting to reëvaluate the clinical significance of Klebsiella in the light of this newer microbiologic information.

To the best of our present knowledge, 77 capsular types of Klebsiella have been described to date. It is obvious that an evaluation of the clinical significance of various Klebsiella types is needed. Edwards and Fife * have recently reported the source of 626 Klebsiella strains according to type. Although the strains most commonly isolated from the respiratory tract are types 1, 2 and 4, whereas the strains most commonly isolated from the urinary tract are types 7 and 19, in this country any type may occur in any clinical situation.

The classic concept of Friedländer's pneumonia includes the idea that the vast majority of cases are due to Klebsiella type 1 (type A of Julianelle). With the new classification of this organism, we have found that type 1

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is rather uncommon in the respiratory tract, and we sometimes see cases of destructive pneumonia associated with Klebsiella strains of higher types. These have occurred often enough to stimulate our interest in the relationship between various types of Klebsiella and various forms of pulmonary disease.

In 1952 and 1953 a comprehensive study of pneumonia at the Philadelphia General Hospital during a six month period revealed 24 patients who had pulmonary disease and Klebsiella in their sputum.5 This number occurred among 283 patients admitted with a diagnosis of pneumonia, and seemed to constitute an unusual prevalence for Klebsiella infections. Analysis of this group of cases revealed similarities to those included in various reports in the literature in the following respects: tendencies to chronicity of disease with delayed resolution, residual cavitation and fibrosis, leukopenia, and a predilection for middle-aged white males. The clinical picture was quite variable, but some cases typical of classic Friedländer's pneumonia were associated with Klebsiella of types other than 1 and 2 (A and B of Iulianelle). We therefore felt that most, if not all, of the cases included were examples of Klebsiella infection of the lungs, despite the fact that several patients appeared to have rather unimpressive patches of pneumonitis associated with pulmonary fibrosis and emphysema, two had tuberculosis, and one a bronchogenic carcinoma. During that six month study there were also two additional patients who yielded Klebsiella in the sputum, one with merely acute pulmonary congestion due to left ventricular failure, and the other with no evidence of respiratory disease.

Since that time a broader experience has led us to believe that the clinical significance of a Klebsiella serotype in the sputum may not always be immediately apparent. We have therefore been interested in surveying the conditions under which various Klebsiella serotypes appear in the respiratory secretions. The following is a preliminary report of our investigations into the rôle of Klebsiella in the respiratory tract.

METHOD AND MATERIAL

A. Sources of Cultures: The Klebsiella strains were isolated from clinical specimens of sputum and bronchial secretions.

B. Identification of Klebsiella: Criteria for designating an organism as a Klebsiella strain were as follows: a gram-negative, nonmotile, aerobic bacillus which fermented lactose, adonitol and inositol and gave positive Voges-Proskauer, citrate utilization and urease reactions and, in addition, was indole- and methyl red-negative. Organisms with this biochemical pattern were then subjected to slide agglutination tests with type-specific capsular antisera prepared for types 1 to 10, inclusive. If the organism was acapsular, it was subcultured on media designed to promote the formation of capsules and mucus.¹⁹ Strains which failed to agglutinate with available sera were simply recorded as Klebsiella species.

C. Antibiotic Susceptibility Tests: A disc procedure was used, as described previously by our group.⁶ Antibiotics tested included streptomycin, chloramphenical and tetracycline.

D. Clinicobacteriologic Correlation: The prevalence of this organism in the respiratory secretions in various categories of individual was determined during the months from November, 1955, to January, 1956. Comparison was made between a group of 147 patients with all kinds of respiratory disease and people without respiratory disease. The latter group consisted of 200 employees and 97 patients scattered throughout the hospital. These individuals were selected so that there was no clinical evidence of respiratory disease, and a chest roentgenogram or photofluorogram was negative. Throat cultures were substituted for cultures of sputum or bronchial secretions in these individuals.

TABLE 1
Nosocomial Prevalence of Klebsiella in the Respiratory Tract

Category	Number Examined	Source	Per Cent with Klebsiella
Employees	200	Pharvnx	2.0
Patients without respiratory disease	97	Pharynx	8.2
Patients with tuberculosis	72	Sputum	8.3
Patients with bronchogenic carcinoma	70	Sputum	11.4
All patients with respiratory disease Patients with respiratory disease on the	147	Sputum	13.7
medical wards	99	Sputum	23.2

For data on correlations in patients with respiratory disease, hospital records were reviewed and, whenever possible, patients and their roent-genograms were examined.

RESULTS

The results of this investigation are presented in tables 1 to 5. Table 1 presents the prevalence of Klebsiella organisms: 2% in employees, 8.2% in patients without respiratory disease, 13.7% in patients with respiratory disease, and 23.2% in patients with respiratory disease on the medical wards. The difference between the prevalence for employees and the prevalence in patients without respiratory disease is statistically highly significant (t=3.32). Also, the difference between the prevalence for patients without respiratory disease and the prevalence for patients with respiratory disease on the medical wards is statistically highly significant (t=2.94). By reviewing the records of patients with tuberculosis and those with bronchogenic carcinoma, we were able to find a number who had had sputum cultures over a period of several years, and the prevalence in these was of the same order of magnitude as the prevalence for patients without respiratory disease: 8.3% of 72 patients with tuberculosis, and 11.4% of 70 patients with bronchogenic carcinoma.

TABLE 2

Distribution	of Types	Among	188	Respiratory

Type	Per Cent
1	3.2
2	8.0
3	0.0
4	2.7
5	0.0
6	0.0
7	3.2
8	3.2
9	2.2
10	0.0
Species	77.5

Table 2 shows the distribution of Klebsiella strains according to capsular type among 188 consecutive respiratory isolations during a 30 month period. Only 22.5% of these strains could be typed with sera for types 1 to 10. The most common of these was type 2, which made up 8% of the total. Types 1, 4, 7, 8 and 9 each constituted approximately 2 or 3% of the total. In this particular series there were no examples of types 3, 5, 6 or 10, but 3 and 6 have been isolated on rare occasions at other times during the past four years. Types 1, 2 and 4 represent 13.9% of the total, so that obviously these classic respiratory strains are a small minority of all strains encountered today with the present system of bacterial classification.

In table 3 there is a comparison of the prevalence of various forms of respiratory disease according to the capsular type of Klebsiella isolated. Thirty-nine cases with types 1, 2 and 4 were compared to 50 cases with higher types of Klebsiella isolated from sputum or bronchial secretions. There are two significant differences between these two groups of patients: (1) Destructive lung disease (abscess and atelectasis) was more than three times as common when the organism was among the lower types than when it was among the higher types. (2) There were no examples of patients without respiratory disease among cases with types 1, 2 and 4, whereas 12% of the cases with higher types of Klebsiella had no evidence of respiratory disease. (This finding is consistent with the fact that our survey of throat cultures in 200 employees and 97 patients without respiratory

TABLE 3

Types of Pulmonary Disease Associated with Klebsiella of Low and High Capsular Types

Category	39 Cases with Types 1, 2, and 4 Per Cent	50 Cases with Higher Types Per Cent		
Pneumonia	31	52		
Destructive	33.3	10		
Lung abscess	23	10		
Atelectasis	10.3	0		
Tuberculosis	13.2	12		
Miscellaneous	22.5	14		
No respiratory disease	0	12		

disease revealed only Klebsiella of the higher types.) Pneumonia was common in both groups, but less common among patients with types 1, 2 and 4, because of the larger number of cases with destructive lung disease. Tuberculosis occurred equally in both groups. Miscellaneous diseases among cases with the lower types included one patient with asthma, four with pulmonary fibrosis, one with bronchogenic carcinoma, and three with pulmonary congestion. In the other group, miscellaneous cases included two patients with acute bronchitis, one with asthma, one with pulmonary infarct, one with a "coin" lesion and two with pulmonary fibrosis.

Table 4 compares the susceptibilities of these organisms as a whole with the susceptibilities of types 1, 2 and 4 with respect to chloramphenicol, streptomycin and tetracycline. Antibiotic patterns of susceptibility are also included. There are no significant differences between organisms of all types and organisms of the lower types. However, susceptibility to chloramphenicol is similar to susceptibility to streptomycin, whereas susceptibility to tetracycline is significantly lower. Therefore, chloramphenicol

Table 4
Susceptibilities of Respiratory Klebsiella Strains

	Per Cent Susceptible			
Antiblotic	188 Strains of All Types	26 Strains of Types 1, 2 and 4		
Chloramphenicol Streptomycin Tetracycline Antibiotic Pattern	81 74 63	73 85 65		
3 drugs 2 drugs 1 drug None	52 25 17 6	54 25 9 12		

or streptomycin would appear to be the drug of choice when susceptibilities are unknown.

Further analysis of the antibiotic patterns reveals that, of 47 strains susceptible to only two antibiotics, 22 were susceptible to both streptomycin and chloramphenicol, 12 were susceptible to chloramphenicol and tetracycline, and nine were susceptible to streptomycin and tetracycline. Of 32 strains which were susceptible to only one antibiotic, 22 were susceptible to chloramphenicol, 13 were susceptible to streptomycin, and only two were susceptible to tetracycline. Of the entire series of 188 strains, 175, or 93%, were susceptible to either streptomycin or chloramphenicol or both antibiotics. Therefore, the in vitro data would suggest that the combination of streptomycin and chloramphenicol might more often be effective than either drug alone when the susceptibilities of the Klebsiella are not known. As yet, we have not accumulated data to support this.

Since many patients with respiratory infections are treated with penicillin without benefit of a pretreatment sputum culture, it has been difficult to accumulate a large series of cases in which the exact relationship of Klebsiella strains of various types to antimicrobial therapy can be pinpointed. Our experience suggests that in those patients who have the usual Grampositive bacterial flora in sputum prior to therapy, the emergence of Klebsiella strains during or after penicillin therapy may be limited to the higher types. Table 5 presents some evidence in favor of this impression.

In 43 cases with Klebsiella in the sputum, serial culture results were available prior to and during therapy with various antibiotics. Fourteen patients showed Klebsiella types 1, 2 or 4, and 29 patients showed Klebsiella of higher types. The number of cases treated with penicillin and the number treated with streptomycin or a broad spectrum antibiotic are indicated in each group, together with the number of patients who presented a Klebsiella prior to therapy, the number of these whose Klebsiella was abolished by therapy, and the number of patients in whom Klebsiella emerged for the first time during therapy. Overlap is due to multiple therapies in some

Table 5
Relation of Klebsiella to Antimicrobial Therapy
According to Capsular Type

Klebsiella Type	Number of Cases	Therapy	Number Treated	Number with Klebsiella Prior to Therapy	Number with Klebsiella Abolished by Therapy	Number in whom Klebsiella Emerged on Therapy
1, 2 and 4	14	Penicillin	4	4	0	0
Higher types	29	Streptomycin or broad spectrums Penicillin Streptomycin or broad	10 22	9	8	1 16
		spectrums	13	7	6	6

patients. From the figures presented, it is apparent that when Klebsiella types 1, 2 and 4 were isolated, they were usually present prior to therapy, whereas many Klebsiellae of higher types emerged for the first time during penicillin therapy or during the administration of another drug to which the organism was resistant. Further, penicillin does not eliminate Klebsiella from the respiratory secretions, and this would be expected from the fact that these organisms are known to be resistant to penicillin. However, streptomycin or broad spectrum antibiotics usually cause the Klebsiella to disappear.

Two patients with Klebsiella of the higher types had no acute respiratory disease and received no antimicrobial therapy, and the Klebsiella appeared some time after admission, having been absent in the initial sputum culture. It is probable that these two cases represent instances of nosocomial spread of the organism from either employees or other patients.

There were seven patients whose Klebsiella emerged for the first time during therapy with streptomycin or broad spectrum antibiotics. Six of

these organisms were of the higher capsular types. Susceptibilities were tested in six, and three were resistant to the antibiotic used. Two strains emerged during therapy with an antibiotic to which they were susceptible, but treatment included concurrent administration of another antibiotic to which Klebsiella is presumed to be resistant: penicillin in one case and Nystatin in the other. The significance of this observation is not entirely obvious unless the administration of a drug to which the organism is resistant diminishes the efficacy of a simultaneously administered inhibitory antibiotic.

We wish to emphasize the fact that a total of 19 of the 29 Klebsiella strains of higher capsular types emerged during therapy with antibiotics to which the organism was resistant. This usually did not occur when the organism was type 1, 2 or 4, but the number is too small to warrant a conclusion.

DISCUSSION

1. Bacteriology of Klebsiella: The historical taxonomic differentiation between Klebsiella pneumoniae and Aerobacter aerogenes has no real foundation in fact. Hay ** suggested that when in 1882 the Friedländer's bacillus was isolated from patients with pneumonia, it was studied primarily from the morphologic standpoint. On the other hand, Escherich, who first described A. aerogenes in 1886, emphasized its close similarity to E. coli. However, more recent investigations point to the fact that, while A. aerogenes is related in some respects to certain strains of E. coli, it is more closely related biochemically and serologically to the classic Friedländer's bacillus.

On the basis of existing criteria in Bergey's Manual. the practical routine differentiation of K. pneumoniae from many strains of A. aerogenes is impossible. The only differentiating characteristic given for these two organisms is motility, the former being described as nonmotile and the latter as either motile or nonmotile. As early as 1905, MacConkey 8 reviewed the literature on B. lactis-aerogenes of Escherich and concluded that this organism had always been considered nonmotile. The excellent statistical study by Levine of in 1918 also showed A. aerogenes to be nonmotile. Thus, on historical grounds, A. aerogenes should be limited to nonmotile forms. In 1929 Edwards 8 reported the morphologic and biochemical similarity between the Friedländer bacillus and cultures which, on the basis of criteria existing at that time, were classified as A. aerogenes. This similarity was so close that, in his opinion, there was no basis for generic differentiation between the two organisms. Other investigators 2, 10, 11, 12, 13, 14 have subsequently confirmed his findings. Julianelle's 15 view that K. pneumoniae and A. aerogenes could be distinguished by their somatic antigens is now untenable in the light of studies by Kauffmann,2 Orskov,16 and Edwards and Fife.17 Therefore, inclusion of these two organisms into a single genus has been advocated, with the additional recommendation that the genus be assigned the name Klebsiella on the grounds of priority.2, 18, 19

This recommendation was adopted in our laboratory, so that the term "Klebsiella infection," as used herein, is to be interpreted as referring to infection by Klebsiella organisms as defined by Kauffmann, regardless of the anatomic site from which they may be isolated. Thus, the Klebsiella group comprised a large group of serologically related Gram-negative, nonsporing and nonmotile rods which usually possess capsules, form mucus, and usually exhibit the biochemical pattern presented under "Method." Although these criteria permit the broad identification of organisms as members of the group Klebsiella, much confusion will be avoided if it is remembered that the classification of bacteria into sharply delineated divisions is dictated by practical necessity. In reality, such divisions are wholly artificial: variations in biochemical pattern occasionally occur, and therefore not all cultures encountered will fall neatly into one or another of these divisions.

Kauffmann 19 has pointed out that Klebsiella may occur in acapsular as well as capsular forms, with or without the formation of mucus. Colony selection and culture on special media permit the isolation of these various forms. From a practical standpoint, the differentiation of members of the Klebsiella genus is accomplished by the identification of capsular serotypes. According to Edwards and Fife, 17 the serologic specificity of Klebsiella capsules was first pointed out by Toennissen in 1912. Julianelle demonstrated types A, B and C in 1926. Types D, E and F were described by Goslings and Snijders in 1936. A large number of additional capsular types have been demonstrated in recent years, a number far in excess of the letters in the alphabet. Therefore, capsular types are now designated by Arabic numerals, so that the classic types A to F are known as types 1 to 6. The number of types now totals 77. Recent investigations 19 indicate antigenic interrelationships between several Klebsiella types and some Escherichia. Because of this and the rapid increase in capsular types of Klebsiella, Henriksen 20 has objected to the adoption of a serologic typing schema for Klebsiella as a routine procedure in the present state of knowledge. In our opinion, his arguments are without merit as contraindications for establishing a classification schema based on Klebsiella serotypes. Further studies will undoubtedly clarify the situation.

With the recent great increase in recognizable capsular types, the identification of Klebsiella by serotype becomes a problem of some magnitude for the laboratory. Each laboratory must decide for itself how much effort it wishes to expend in typing these organisms. At the Philadelphia General Hospital, current facilities permit only types 1 to 10 to be identified. Those strains for which specific capsular sera are lacking are designated Klebsiella species, pending more definitive identification by a reference laboratory equipped for this purpose.*

^{*}The Communicable Disease Center, U. S. Public Health Service, Chamblee, Georgia. We wish to acknowledge the invaluable aid and advice given us by Dr. P. R. Edwards, as to both preparation of typing sera and typing of cultures.

2. The Carrier State: It is difficult to draw comparisons with much of the older literature because of changing bacteriologic concepts. According to Obrinsky et al.,²¹ Klebsiella occurs in the carrier state in less than 1% of patients without respiratory disease, but Hyde and Hyde ²² state that it has been found in the throats in over 5% of normal individuals. However, these authors do not define the organism to which these statements refer. The assignment of clinical significance to this organism in the respiratory tract must take this into consideration. It is of interest that in 1920 Bloomfield ²³ was unable to implant Friedländer's bacillus in the throats of normal individuals so as to produce a carrier state, or infection. On the other hand, he was able, repeatedly for months, to culture Friedländer's bacillus from the throats of two subjects without respiratory disease. In

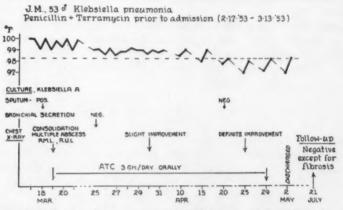
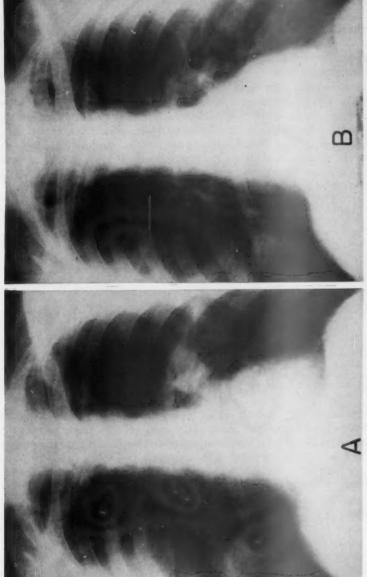


Fig. 1. Case of destructive pneumonia with Klebsiella type 1 (or A) in the sputum. Gradual clinical and roentgenographic (see figure 2) improvement occurred on therapy with ATC (1 gm. each of oxytetracycline, chlortetracycline and chloramphenicol daily in divided doses).

conjunction with our findings in throat cultures of employees and patients without overt respiratory disease, these observations have two implications: First, in the presence of respiratory disease the isolation of Klebsiella may have no clinical significance at that particular time. Second, the pathogenic rôle of Klebsiella in the respiratory tract may depend to a great extent on the existence of appropriate conditions in the host so as to favor a state of infection and disease. To pursue this line of reasoning further, it is possible that, although at any given time a Klebsiella may be present in the respiratory tract without producing overt disease, if the organisms persist a time may come when host resistance may break and the commensal state may erupt into full fledged disease.

3. The Clinical Significance of Klebsiella Types: In the past, those clinical studies of Friedlander's pneumonia which have included capsular typing



Initial and final chest roentgenograms of patient J. M., whose clinical course is illustrated in figure 1. A illustrates trilobar pneumonia with bilateral cavitation on admission. B shows residual fibrosis at end of hospital course. 3 FIG.

of the organism have emphasized the importance of Type 1 (or A, of Julianelle). (Case J. M., figures 1 and 2, is an example.) Various reports have implicated type 1 in from 73% to 100% of the cases.²² In the light of recent work one wonders whether this is due to selection of cases according to the ability of the laboratory to type the organism. In view of our present improved knowledge of these bacteria, it is obvious that type 1 is seldom isolated from the respiratory tract. If all instances of so-called Friedländer's pneumonia were due to type 1, this entity would indeed be rare. The clinical hallmark of this disease is destructive pneumonia characterized by abscess formation, atelectasis, or both. At this institution, such disease has been encountered frequently in association with types 2 and 4, as well as type 1 Klebsiella. Therefore, in view of the paucity of type 1 organisms, cases with any one of these three types have been included in a single group for comparison with cases associated with Klebsiella of higher types in the respiratory secretions.

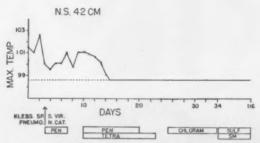
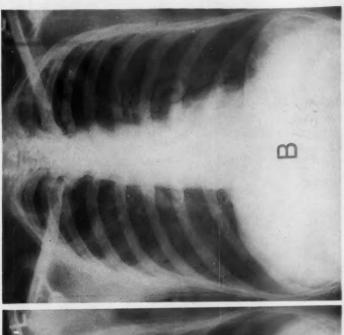


Fig. 3. Case of destructive pneumonia with Klebsiella species and pneumococcus in the sputum on admission. No clinical response occurred to penicillin. When tetracycline was added on the tenth day, response was prompt. Because of the persistence of cavitation, a trial of chloramphenicol and, later, sulfadiazine with streptomycin was made (see figure 4).

Our analysis indicates that Klebsiella may be found in all sorts of clinical conditions of the respiratory tract. However, we have rarely encountered types 1, 2 or 4 in individuals without any respiratory disease, whereas higher types are sometimes encountered in such persons. Sometimes the lower types are seen in individuals who have emphysema and chronic bronchitis or similar types of afebrile bronchopulmonary disease, including tuberculosis and carcinoma. Sometimes such persons have shown symptomatic improvement on proper antibiotic therapy directed against the Klebsiella organism. Such observations have been reported by Fulton and McKinlay 24 in a small number of cases.

It is significant that one third of patients with Klebsiella of lower types have destructive lung disease. By comparison, such disease is uncommon in patients with Klebsiella of the higher types, but it does occur. (Case N. S., figures 3 and 4, is an example.)



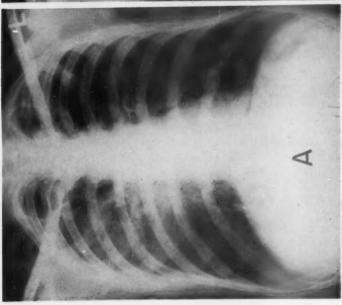


Fig. 4. Initial and final chest roentgenograms of patient N. S., whose clinical course is illustrated in figure 3. A shows confluent bronchopneumonia with cavity in the right lung and a small area of infiltration in the left upper lobe. B shows a small amount of residual fibrosis at the end of the hospital course.

On the basis of circumstantial evidence accrued to date, and of the studies of others such as Weinstein, 25, 27 it seems that the appearance of many Klebsiella strains of higher types can be correlated with prior or concurrent therapy with narrow spectrum antimicrobial drugs, particularly penicillin. In most of these instances the respiratory infection responds to penicillin, and therefore it would appear that the Klebsiella organism has no special clinical significance at the time, but rather represents part of the residual antibiotic-resistant flora that remains after the susceptible organisms are abolished by therapy. This explains much of the high prevalence of Klebsiella in the sputum of patients on the medical wards. However, occasionally we see superinfection with Klebsiella, and such an occurrence must be kept in mind when, after initial response to penicillin, the patient's con-

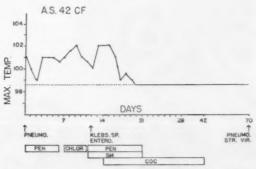
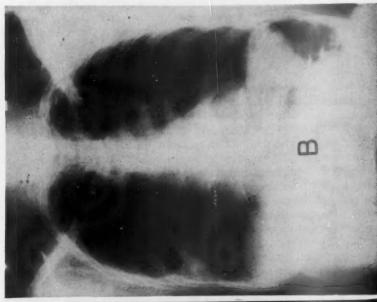


Fig. 5. Case of pneumonia due to pneumococcus, showing an initial clinical response during the first three days of penicillin therapy, followed by worsening, despite a change in therapy to chlortetracycline (CHLOR). The sputum then contained a Klebsiella species and enterococcus, the former being resistant to chlortetracycline. No response occurred on therapy with penicillin and streptomycin, but response was prompt after the addition of COC (same broad spectrum combination which was designated ATC in the case of J. M., figure 1). See figure 6 for roentgenograms.

dition worsens and he responds again only when treatment is instituted with a drug to which the Klebsiella is susceptible. (Case A. S., figures 5 and 6, is an example.)

At present, the evaluation of the rôle of a Klebsiella in a patient's illness can be made often only in retrospect, and only if the case has been well studied from the onset of medical care. This is due to the fact that there is no specific test for Klebsiella disease. Consequently a state of confusion often exists during the management of the case, a state which is enhanced by the present-day tendencies to use shot-gun therapy in patients who do not show an immediate response to penicillin. Thus, many individuals receive a broadside of antimicrobials with the vague hope that one drug will justify the adjective "miracle." Such action, of course, heaps confusion upon confusion, and analysis of many cases leaves the observer with



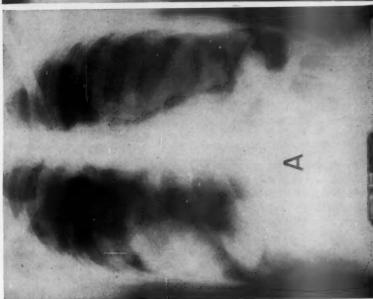


Fig. 6. Initial and final chest roentgenograms of patient A. S., whose clinical course is illustrated in figure 5. A shows bilateral pneumonia on admission. B shows the development of cavitation, resolution of the pneumonia with persistence of cavitation at the end of the hospital course. This is an example of superinfection with a Klebsiella species.

the question as to whether the patient might have done as well with no therapy at all. At present, the assessment of clinical significance for a given organism isolated from the patient must depend largely on the ensemble of the case, including adequate pretreatment studies and serial studies during therapy, combined with intelligent use of antimicrobials so that the effective drug can be recognized. Otherwise, experience yields no rewards.

Thus, in the initial study of a patient with pulmonary infection, if Klebsiella is isolated in conjunction with other known pathogens, such as the pneumococcus, usually the disease will respond to penicillin, as pointed out by Ogilvie. This does not mean that the Klebsiella necessarily plays no clinical rôle. Further studies of such cases are needed to clarify the situation. On the other hand, occasionally such a patient shows no response to penicillin and then improves promptly on a broad spectrum antibiotic to which the Klebsiella is susceptible. Under such conditions it is probable that the Klebsiella is the primary pathogen, and we have seen such cases with Klebsiella types other than 1, 2 or 4 (case N. S., figures 3 and 4).

In general, it appears that the clinical picture associated with the presence of Klebsiella is protean. Those cases which fit the classic concept of Friedländer's pneumonia constitute no real problem in evaluation, but they are uncommon. More often one sees cases in which assessment of a Klebsiella is difficult and further investigation is needed.

4. Antibiotic Susceptibilities: The in vitro results reported herein indicate that either streptomycin or chloramphenicol should receive primary consideration as the drug of choice for Klebsiella infection. To go one step further, 93% of all strains were susceptible to either drug, or both, tested as single agents. This suggests that it might be well to use both drugs in treatment, at least until the susceptibility pattern for the particular organism is reported from the laboratory. The capsular type of Klebsiella may be a factor in susceptibility, although the number of organisms composing the group of lower types was too small to permit definite conclusions.

SUMMARY AND CONCLUSIONS

Klebsiella pneumoniae and Aerobacter aerogenes cannot be distinguished on any basis. Since 1952, organisms fitting the criteria of Kauffmann have been designated Klebsiella in our laboratory, and members of this group have been differentiated by capsular type. Serotypes 1 to 10 have been distinguished. Our preliminary studies of the significance of this organism in the respiratory tract are reported here in relation to capsular type and antimicrobial therapy.

Klebsiella is found in the throats of employees and patients without respiratory disease, as well as in the sputum of patients with respiratory disease. It is concluded that Klebsiella may occasionally be present in the respiratory tract without causing clinical disease at the time the organism is isolated.

Those strains which can be typed with sera for capsular types 1 to 10 compose a minority of the strains isolated, and the classic respiratory types 1, 2 and 4 are uncommon. The latter are associated in one third of the cases with destructive lung disease, whereas higher types are seldom found in such patients. Usually only the higher types have been found in persons without respiratory disease. However, in patients with respiratory disease any type of Klebsiella may be isolated from patients with any type of pulmonary disease.

The majority of Klebsiella strains are of types higher than 1, 2, and 4, and a majority of the higher types are isolated from patients treated with penicillin or another drug to which the organism is resistant. In most such instances the Klebsiella does not seem to be pathogenic, but occasionally it may give rise to superinfection.

In vitro studies of Klebsiella susceptibility suggest that streptomycin and chloramphenicol are the drugs of choice. Ninety-three per cent of strains are susceptible to one or both of these antibiotics.

SUMMARIO IN INTERLINGUA

Studios bacteriologic—pauco cognoscite in circulos clinic—ha indicate que species de klebsiella e Aerobacter aerogenes es indistinguibile e que le inclusion de iste organismos in un gruppo unic, le gruppo de klebsiella, es justificate. Il es possibile differentiar varie stirpes intra le gruppo super le base de lor reactivitate serologic capsular. Usque nunc, 77 typos capsular ha essite demonstrate. Con iste information e per medio de seros que differentia le typos 1 a 10, un studio super le relation inter species de klebsiella e morbo pulmonar ha essite in progresso durante le passate quatro annos al Hospital General de Philadelphia.

Le prevalentia nosocomial del organismos mentionate variava a iste institution ab 2% in le secretiones pharyngee del empleatos a 13,7% in le sputo de patientes con omne genere de morbo respiratori. Patientes sin obvie morbos respiratori habeva le mesme organismos in lor secretiones pharyngee con un frequentia de 8,2%.

Le majoritate del stirpes respiratori de species de klebsiella non es typisabile per medio del seros pro le typos ab 1 a 10. Ex le 22,5% que se provava typisabile, le plus commun es typo 2 (8%). Plus basse procentages esseva trovate pro typos 1, 4, 7, 8, e 9.

Le morbo pulmonar que es associate le plus frequentemente con le presentia de klebsiella in le sputo es pneumonia. Le typos 1, 2, e 4 se associa con destructive morbos pulmonar (abscesso e atelectasis) plus frequentemente que le typos a numeros plus alte. De facto, le typos superior se trova a vices in patientes sin morbo respiratori, in contrasto con le typos 1, 2, e 4.

Le investigation del susceptibilitate a antibioticos in le casos de 188 stirpes respiratori revelava que 81% esseva inhibite per chloramphenicol, 74% per streptomycina, e 63% per tetracyclina. Le susceptibilitates de 26 stirpes del typos 1, 2, e 4 es simile. Le configuration del susceptibilitate a antibioticos es etiam simile.

Circa un medietate del stirpes de klebsiella isolate ab patientes qui non recipe cursos de penicillina es del typos 1, 2, e 4, durante que quasi omne le stirpes isolate ab patientes recipiente penicillina es del typos superior. Le relation inter typo capsular e therapia a penicillina require investigationes additional pro elucidar le mechanismo implicate in illo.

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THE METABOLISM OF FOLIC ACID IN CIRRHOSIS *

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THE prevalence of macrocytic anemia in patients with chronic liver disease has suggested to many observers that liver damage disturbs hematopoiesis by altering the storage or the metabolism of one or more of the substances effective in the treatment of pernicious anemia.1-4 However, it has been observed that most cases of the macrocytic anemia of liver disease bear little resemblance to pernicious anemia morphologically, and generally do not respond to liver extract.5,6 Moreover, extracts prepared from the livers of patients with the anemia of liver disease have been found to possess antipernicious anemia activity. Nevertheless, apparent hematologic responses to liver extract, yeast, ground beef and vitamin B12 have been reported in certain patients with cirrhosis and anemia, in some of whom megaloblastic bone marrows in association with free gastric hydrochloric acid were observed.2, 8, 6, 8 Thus, the possibility has remained that chronic liver disease does interfere with the metabolism of one or more of the substances necessary for normal hematopoiesis, although this defect may be demonstrable only in unusually severe cases. The present study, which was reported in preliminary form elsewhere,9 concerns a group of patients with cirrhosis associated with chronic alcoholism, in whom certain aspects of the metabolism of folic acid, citrovorum factor, vitamin B12 and ascorbic acid were investigated.

METHODS

Observations were carried out in a special metabolic ward upon a group of 16 patients with cirrhosis associated with chronic alcoholism. There were eight patients of each sex whose ages ranged from 28 to 64 years. diagnosis of Laennec's cirrhosis was made clinically, and in eight instances it was verified pathologically. These patients showed various degrees of anemia, generally macrocytic in character and not associated with evidence of current or of previous blood loss. Each patient was observed for at least 10 days on a controlled diet before the administration of hematopoietically active material.

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Red cell counts and hemoglobin and hematocrit levels were determined every three or four days, and reticulocytes were enumerated every day, by standard procedures.¹⁰ A detailed presentation of the hematologic findings on these patients, with particular reference to the hemolytic process involved, has been published elsewhere.11

The folic acid activity of materials administered and of specimens excreted was assayed by means of the growth response of Lactobacillus casei ATCC 7469.12 Shortly after their preparation or collection, specimens were stored at -20° C. until the time of assay. The accuracy of the assay method was determined periodically during these observations by measuring the recovery of known amounts of synthetic folic acid (pteroylglutamic acid: PGA) added to samples of the material under study. There was a mean recovery of 103% (range: 96 to 110%) of added PGA. The folic acid activity of natural materials was determined before and after incubation at 37° C. for 20 hours with a homogenate of chick pancreas conjugase * buffered at pH 7.4. Twenty milligrams of chick pancreas were added to each gram of test material.18 Activity for L. casei prior to treatment with conjugase will be referred to as "free" folic acid, and that activity liberated by enzymatic hydrolysis will be designated as "conjugated" folic acid.

Citrovorum factor (CF) activity was assayed with Leuconostoc citrovorum ATCC 8081 by the method of Sauberlich.14, 15 CF activity is recorded as the equivalent of natural CF rather than of the synthetic racemic mixture † which was employed as the assay standard and which possesses only 50% of the potency of the natural form.

The serum level of vitamin B₁₂ was assayed by a modification ¹⁶ of the method of Ross,17 which utilizes the specific growth response of the flagellate Euglena gracilis. Results are reported as total vitamin B₁₂ concentration, which includes free and protein-bound moieties.

The level of reduced ascorbic acid in the buffy coats of venous blood specimens was determined by the method of Butler and Cushman.18

MATERIALS

Solutions of PGA for oral and for parenteral administration were prepared in pH 7.4 phosphate buffer from crystalline PGA or from solutions of sodium folate.‡ The dosage of folic acid is here expressed in terms of activity for L. casei; and the sodium folate solutions employed were found to contain an average of 24.9 mg. per cubic centimeter, rather than 15.0 mg. per cubic centimeter, as described by the manufacturer.

A vacuum-dried extract of brewer's yeast § was used as a source of

^{*}Bacto-chicken pancreas, Difco Laboratories, Inc., Detroit, Michigan.
† "Leucovorin," generously supplied by Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

‡ "Folvite," generously supplied by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

§ Yeast extract, type 3, Standard Brands, Inc., New York, N. Y.

natural folic acid in both the conjugated state (yeast A) and the free state (yeast B). Deconjugation of the folic acid in yeast B was performed, as in the assay of conjugated folic acid, by incubating the buffered yeast solution at pH 7.4 at 37° C. for 20 hours with chick pancreas. No significant further increase in free folic acid activity of the samples occurred upon subsequent repetition of this procedure using fresh conjugase. The chick pancreas preparation was found to possess activity for L. casei equivalent to 19.5 millimicrograms per milligram; this activity was competitively inhibited by aminopterin in a 1:1 ratio to chick pancreas folic acid activity. Consequently, yeast A, as a source of conjugated natural folic acid, was prepared in the same fashion as yeast B, except that the chick pancreas conjugase was heat-inactivated by autoclaving before its incubation with the yeast. Subsequent assays determined that the folic acid activity of yeast A was 10% in the free and 90% in the conjugated form, while that of yeast B was entirely in the free form. After deconjugation, 30.7% of the folic acid activity of the yeast was found to be nondialyzable. Aminopterin competitively inhibited the folic acid activity of both yeast preparations for L. casei. The controlled diet on which most of the patients remained throughout these studies contained an average of 560 µg of folic acid, 9% in the free state, and was very low in vitamin B12. Only varying fractions of the diet were actually ingested.

RESULTS

The 16 patients studied fell clearly into two groups from the standpoint of blood morphology. The first group consisted of 12 patients, whose hemoglobin levels ranged from 5.1 to 13.6 gm.%. The anemia in these patients was associated with mild to moderate macrocytosis, and with bone marrows containing largely normal red cell and white cell precursors. These 12 patients were given synthetic folic acid (PGA) in amounts ranging from 0.25 to 10.0 mg. daily for 10-day periods. Administration was by the oral route in five cases and by the parenteral route in seven. In no instance was there a reticulocyte response or a rise in hemoglobin level. As may be seen in table 1, urinary folic acid activity prior to therapy in the six of these patients who were studied averaged 3.49 µg per day (range of mean values: 1.63 to 5.82), as compared with the mean values for eight normal men ranging from 1.58 to 5.94 µg per day, with an average value of 3.93 µg. Following daily administration of synthetic folic acid either orally (subjects 1, 2 and 3) or parenterally (subjects 4, 5 and 6), maximal urinary folic acid levels were generally reached by the second day of therapy. Five of these six patients subsequently received parenteral Leucovorin (synthetic CF) for 10 days, in amounts ranging from 0.5 to 3.0 mg. daily. Again in no instance was there a rise of reticulocyte or hemoglobin values. A hemolytic process corresponding in activity to the severity of the anemia was shown to be present in these patients.11

The four patients in the second group stood apart from the others because of the greater severity of anemia, the more pronounced macrocytosis, and the markedly disturbed maturation of red cell and white cell precursors in their bone marrows. Whereas mildly abnormal red cell precursors with certain of the features found in pernicious anemia were occasionally present in the other 12 patients, the bone marrows of these four subjects showed

TABLE 1
Urinary Folic Acid and CF Excretion in Patients with Cirrhosis and Anemia

Subject Admission Hemoglobin Gm.%		Base Line Uri	nary Excretion	Folic Acid	Appearance of Maximal Urinary	Hematologic
	Folic Acid µg/day	CF µg/day	Administered µg/day	Levels of Folic Acid (Days of Therapy)	Response to Folic Acid	
normal men	-	3.93 (1.58–5.94)	0.42 (0.12-0.91)	1,500	1-3	_
	Gr	oup 1: Patien	ts with Norm	oblastic Marro	ows	
1	10.5	3.41 (3.00-3.84)	0.70 (0.41-1.18)	10,000	1	0
2	9.8	4.93 (3.15–9.92)	-	1,000	1	0
3	6.7	2.75 (1.21–6.53)	0.45 (0.38-0.50)	5,000	2	0
4	10.5	2.42 (2.07-3.10)	-	500	2	0
5	9.0	5.82 (4.08–8.40)		250	2	0
6	9.9	1.63 (0.94–2.88)	0.45 (0.19–1.03)	500	3	0
	G	roup 2: Patie	nts with Meg	aloblastic Mar	rows	
1	5.4	0.82 (0.30–1.57)	0.17 (0.05-0.30)	500	16*	+
2	2.9	0.51 (0.33-0.62)	0.11 (0.06-0.16)	250	21	+
3	4.6	2.52 (0.40–4.70)	0.09 (0.05-0.12)	1,500†	33	+
4	5.7	1.60 (0.90-2.30)	0.14 (0.12-0.15)	1,500†	33	+

^{*} A "normal" excretion of the administered PGA was not attained.

pronounced abnormalities of red cell maturation, giving their marrows a clearly megaloblastic appearance. In addition, these marrows showed markedly abnormal granulocyte precursors. All four patients had normal oral glucose tolerance curves, and normal stool fat contents following controlled fat intakes. Except in case 2, roentgenographic studies of the gastrointestinal tract were normal. The average urinary folic acid excretion of these patients during the base line period prior to therapy was 1.38 µg per

[†] Administered as oral yeast extract (see text).

day, with mean values ranging from 0.51 to 2.52 μ g (table 1). The mean daily urinary CF levels during this period averaged 0.13 μ g and ranged from 0.09 to 0.17 μ g. This contrasts with the average value of 0.42 μ g per day for eight normal subjects, and of 0.53 μ g per day for three of the 12 patients with normoblastic marrows. All four patients with megaloblastic marrows responded clinically and hematologically to folic acid preparations. Their individual case histories are presented below:

CASE REPORTS

Case 1. A 41 year old white male chronic alcoholic with moderately severe cirrhosis entered the hospital because of weakness, dysphagia, and edema of the legs. He gave a normal dietary history except for the daily ingestion of about 400 c.c. of ethanol until one month before entry. At that time his food intake was reduced to one or two meals daily, and these consisted of bread, meat, eggs, milk and fruit. Physical examination revealed pallor, obesity, glossitis, enlargement of the liver and spleen, and edema of both legs. Blood examination showed a severe macrocytic anemia, with a red cell count of 1.42 million/cu. mm., a hemoglobin of 5.4 gm.% and a hematocrit of 16.3%. The MCV was 115 μ^8 and the MCHC 33%. The bone marrow was richly cellular and manifested marked abnormalities of myeloid and erythroid maturation similar to those found in pernicious anemia. The gastric juice contained free hydrochloric acid. Tests indicated impaired hepatic function, and a liver biopsy revealed Laennec's cirrhosis. Following a 10-day period in the hospital on a controlled diet containing little or no vitamin B₁₂, the patient was given 500 µg of PGA subcutaneously daily for 18 days. This therapy was associated with a striking reticulocyte response, which reached a maximum value of 26.3% on the sixth day of therapy and was attended by a rise in the hemoglobin level. Beginning on the nineteenth day, the daily administration of 500 µg of Leucovorin subcutaneously for eight days did not produce a second reticulocyte rise. Urinary folic acid activity increased from an average of 0.82 µg per day prior to PGA therapy to reach a plateau level of 12.5 µg per day after 16 days of therapy. However, a normal excretion, as defined below, was not attained during 26 days of treatment which had provided 9.0 mg. of PGA and 4 mg. of Leucovorin.

Case 2. A 48 year old white male chronic alcoholic had been on a grossly deficient diet for at least four or five months before admission. He suffered from cheilitis, glossitis, dysphagia and proctitis, as well as from manifest clinical scurvy. Further details of this case have been reported elsewhere. 19 Blood examination showed that the patient had a severe macrocytic anemia, with a red cell count of 0.71 million/cu. mm., a hemoglobin of 2.9 gm.%, and a hematocrit of 9.2%. The MCV was 130 μ^8 and the MCHC, 32%. The bone marrow was hyperplastic and consisted largely of red cell and white cell precursors with abnormalities of maturation resembling those seen in pernicious anemia. Free hydrochloric acid was present in the gastric juice. The results of liver function tests were abnormal, and a liver biopsy revealed Laennec's cirrhosis. Roentgenographic examination of the gastrointestinal tract shortly after admission revealed "puddling" of the barium and thickening of the mucosal pattern of the duodenum and jejunum. These changes disappeared following therapy. While receiving 250 µg of PGA subcutaneously daily, the patient developed a reticulocyte response which reached a peak of 22.0% on the tenth day of therapy. This reticulocyte rise was followed by an increase in urinary folic acid activity from the base line average level of 0.51 µg per day to an average of 5.14 µg

per day after 21 days of therapy, as indicated in table 1.

Case 3. A 50 year old white female chronic alcoholic entered the hospital com-

plaining of weakness, dizziness, soreness of the tongue, dysphagia and shortness of breath. She had increased her daily ethanol consumption to about 400 c.c. in the previous year, and had limited her food intake to the irregular ingestion of meat and sandwiches. On entry she was pale and possessed an enlarged liver. Blood examination showed a severe macrocytic anemia, with a red cell count of 1.34 million/cu. mm., a hemoglobin of 5.7 gm.%, and a hematocrit of 19.1%. The MCV was 143 $\mu^{\rm a}$ and the MCHC, 30%. There were numerous red cell and granulocyte precursors in the marrow possessing abnormalities of maturation. The gastric juice contained free hydrochloric acid. Liver function was impaired, and a liver biopsy showed Laennec's cirrhosis. This patient and the fourth patient were studied simultaneously, and the results are reported together below.

Case 4. A 61 year old white widow entered the hospital with weakness, pallor and shortness of breath. She had been an alcoholic for many years, and for at least several months her diet had consisted largely of milk, eggs, toast and wine. Physical examination revealed pallor and hepatomegaly. Blood examination showed a severe macrocytic anemia, with a red cell count of 0.96 million cu. mm., a hemoglobin of 4.6 gm.%, and a hematocrit of 15%. The MCV was 156 μ^8 and the MCHC, 31%. The bone marrow contained numerous abnormal red cell and granulocyte precursors which resembled those encountered in pernicious anemia. There was free hydrochloric acid in the gastric juice, and liver function test revealed impaired function.

Observations made on cases 3 and 4 are presented in figures 1 and 2, respectively. Both patients developed spontaneous reticulocyte rises while on a meat-free diet, which provided up to about 100 µg of free and 1200 µg of conjugated folic acid daily as determined with L. casei. Actually, only a small fraction of this diet was ingested by the patients. During these spontaneous reticulocyte responses, mean daily urinary folic acid excretions of 1.60 and 2.52 µg daily, respectively, were observed. Both patients were then given orally for 14 days amounts of yeast A which contained 1,350 μg of conjugated and 150 μg of free folic acid daily, divided into three equal preprandial doses. Both patients showed striking reticulocyte response, followed by increasing hemoglobin levels. There was no associated rise in urinary folic acid or citrovorum factor activity. A subsequent 11-day course of yeast B containing 1,500 μg of folic acid, all of which had been "deconjugated," led to no further rise in reticulocyte levels or in urinary folic acid or citrovorum factor levels. Following this, the oral administration of equivalent amounts of synthetic folic acid (PGA), given in an identical manner, failed to produce a further hematologic response in either patient but did result in each patient in a prompt and progressive increase in urinary folic acid activity, which reached the normal range for that dosage of folic acid on about the ninth and on the eighth day, respectively, of this therapy.

These observations necessitated for their proper interpretation more detailed information than was available as to the normal urinary excretion of folic acid at various dosage levels. Studies of one normal subject whose stools, after incubation with chick pancreas conjugase, contained an average of 219 µg of folic acid daily (range: 95 to 412) revealed that no detectable increase in stool folic acid activity occurred following the parenteral administration of a single dose of 50 mg. of PGA. Consequently, the possibility appeared that the actual absorption of natural folic acid in a given normal subject can be estimated by comparison of urinary folic acid excretion values with those of an oral or parenteral dosage-urinary excretion curve. For this purpose, two normal men were given assayed amounts of PGA subcutaneously in single daily injections for two days and subsequently in thrice-

divided preprandial doses for two days. The urinary excretion of folic acid in these subjects during these injection periods was determined at six different dosage levels, ranging from 180 to 8,200 µg of PGA daily. In subsequent observations on the same normal subjects, the urinary folic acid excretion values following oral administration of PGA, as well as of the

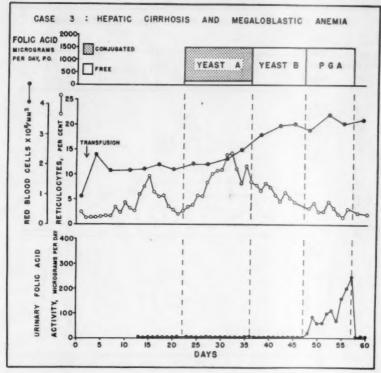


Fig. 1. Observations on the responses of case 3 to various folic acid-containing preparations. Following a spontaneous reticulocyte rise during the period of basal diet the patient developed a second reticulocyte response and increasing hemoglobin levels while receiving a natural source containing 1,500 µg of folic acid (yeast A), 90% of which was conjugated. No further hematologic response attended therapy with enzymatically deconjugated natural folic acid (yeast B) or synthetic folic acid (PGA). Urinary folic acid excretion remained subnormal until about eight days after the administration of synthetic folic acid.

folic acid-containing preparations (yeast A and yeast B) given cases 3 and 4, were also determined. The data are presented in figure 3. In comparisons of urinary folic acid excretion following administration of oral and of parenteral preparations of the various forms of folic acid, the findings indicate that at the dosage level employed, about 25% of naturally occurring folic acid (yeast A) was actually absorbed from the gastrointestinal tract,

whereas about 60% of the natural folic acid after "deconjugation" (yeast B) and over 95% of the synthetic folic acid (PGA) were absorbed. Following oral administration of a mixture of equal amounts of yeast B and synthetic folic acid, the urinary folic acid activity equaled that predicted if each source of folic acid had been absorbed additively and independently.

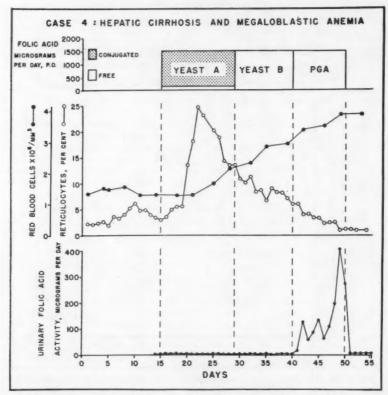


Fig. 2. Observations on the responses of case 4 to various folic acid-containing preparations. A spontaneous small increase in reticulocyte activity occurred during the period of basal diet, after which the administration of a natural source of folic acid (yeast A) was attended by a striking reticulocyte response and increasing hemoglobin levels. No further hematologic response attended therapy with deconjugated folic acid (yeast B) or with synthetic folic acid (PGA).

The serum levels of vitamin B_{12} were measured in 29 patients with cirrhosis, a group which included the 16 patients described. Twenty-one had the "anemia of liver disease" with no evidence of blood loss. Four, as described above, showed megaloblastic changes of the marrow. The mean total serum vitamin B_{12} level of the entire group was 714 ± 534 (one S. D.)

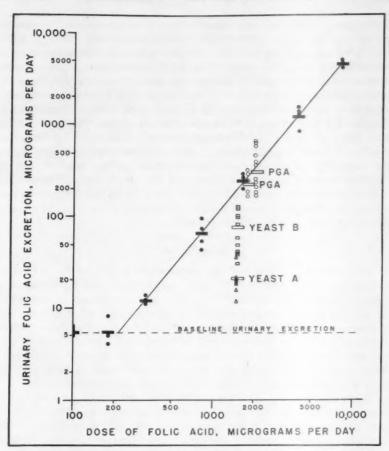


Fig. 3. Relation between intake and urinary excretion of folic acid in two normal men. Solid black circles represent the daily urinary output of folic acid at various dosages of PGA administered subcutaneously. Empty circles depict the urinary excretion of folic acid after the ingestion of conjugated folic acid (yeast A), and empty squares, the daily output following the ingestion of deconjugated yeast folic acid (yeast B). The mean values are represented in each instance by horizontal bars. All preparations were administered prepandially in thrice-divided doses. It should be noted that a log-log scale has been employed.

μμgm per cubic centimeter, as compared with the normal mean of 532 ± 161 . The serum vitamin B_{12} levels of the four patients with megaloblastic anemia in association with liver disease were, respectively, 193, 368, 454 and 557 μμgm per cubic centimeter, with a mean value of 393 μμgm. This contrasts sharply with the serum vitamin B_{12} levels in 33 patients with pernicious anemia, which ranged from 0 to 85 μμgm per cubic centimeter, with a mean of 39.16 It is to be noted that the average serum vitamin B_{12} level of the

29 patients with cirrhosis was increased to 714 μμgm per cubic centimeter by the inclusion of five patients with values, respectively, of 1277, 1376, 1640, 1932 and 2200 μμg per cubic centimeter, as compared with a mean of 496, excluding these five levels. Four of these five patients were anemic, but none manifested clinical or hematologic signs of folic acid deficiency.

The ascorbic acid content of the peripheral blood buffy coat was determined in 16 patients with cirrhosis and anemia. Ascorbic acid activity was absent in 11, three of whom had megaloblastic marrows. Only one of the latter (case 2) had signs of clinical scurvy, consisting of perifollicular petechiae, follicular hyperkeratosis, fragile corkscrew hairs, and hypotension. The remaining 10 patients with no buffy coat ascorbic acid showed no clinical evidence of scurvy, and during the control period in eight of these patients ascorbic acid appeared in the venous blood buffy coats without ascorbic acid therapy. Two of the 11 patients were given 1 gm. of ascorbic acid orally daily, with no reticulocyte response.

DISCUSSION

The evidence that folic acid deficiency existed in four of the 16 patients with macrocytic anemia and cirrhosis lies in their striking hematologic responses to folic acid associated with prompt improvement in appearance and appetite and, in two patients, with rapid disappearance of glossitis and dysphagia. In addition, in these four patients the base line urinary levels of folic acid were low or low normal, and prolonged administration of folic acid was necessary before normal urinary excretion occurred. That associated vitamin B₁₂ deficiency was not a significant factor in these four patients is indicated by their normal serum vitamin B₁₂ concentrations.

Minor abnormalities in the maturation of red cell precursors were present in several cirrhotic patients who did not subsequently respond to folic acid; these changes consisted of increases in size and mild disturbances in the chromatin pattern of some of the early erythroblasts. However, striking morphologic abnormalities of the granulocytes as well as of the erythroid elements in the four patients who did respond were definitive in distinguishing those cirrhotic patients who responded to folic acid from those who did not. Here, too, as in experimental folic acid deficiency in animals, 20, 21 a severe impairment of granulocyte production was characteristic, and gave an impression of greater relative severity than is generally encountered in pernicious anemia. Differential marrow cell counts (1,000 cells) were therefore carried out "blind" on these four patients with cirrhosis and megaloblastic anemia, and on four patients with pernicious anemia of comparable severity.* There were no important morphologic differences between these two groups of patients. As indicated in table 2, an average of 28% of the myeloid cells and 63% of the erythroid cells of the marrows of

^{*}We are indebted to Miss Geneva Daland for making these morphologic examinations, and for her generous assistance throughout this study.

patients with cirrhosis and folic acid deficiency showed defective maturation, while in four comparable patients with pernicious anemia 23% and 71% of the myeloid cells and erythroid cells, respectively, were abnormal. It is not possible on purely morphologic grounds to distinguish the deficiency syndrome described herein from coincident pernicious anemia and cirrhosis.

The coexistence of folic acid deficiency in four of 16 patients represents a remarkably high incidence for this community. In the absence of the sprue syndrome, megaloblastic anemia not associated with significantly low serum vitamin B_{12} levels, and completely responsive to folic acid administration, has been seen by the authors only in certain cases of the "pernicious anemia of pregnancy." In both situations, histories of inadequate diets have usually been present, although in both situations the diets have not always been significantly different from those of comparable patients with-

Table 2

Comparative Blood Morphology in Folic Acid Deficiency Associated with Cirrhosis and in Pernicious Anemia

Diagnosis		Peripheral Blood				Bone Marrow		
	RBC ×10 ⁴ / mm. ³ Hgb. Gm.%		MCV µ3	MCHC Gm.%	WBC ×10 ³ /	M/E Ratio	Percentage of Cells with Abnormal Maturation	
				mm.*		Myeloid	Erythroid	
Folic acid de- ficiency and cirrhosis (4 patients)	1.21 (.96- 1.42)	5.0 (4.4– 5.7)	134 (115– 156)	31 (30–33)	3.5 (1.4– 5.8)	2.3 (2.0- 3.0)	28 (17–37)	63 (45–79)
Pernicious anemia (4 patients)	1.35 (1.23– 1.47)	5.5 (4.8– 6.5)	125 (116– 132)	32 (30–34)	5.7 (2.1- 7.4)	2.4 (1.3- 3.5)	23 (17–28)	71 (66–76)

out megaloblastic anemia. Occasionally, as in the first of the four patients reported here, relatively normal dietary histories have been elicited.

In the absence of a clearly defined or consistently present dietary deficiency of folic acid, the possibility of a defect in folic acid absorption was considered. The results of oral glucose tolerance tests and stool-fat excretions following periods of controlled high fat intake were normal. The ability to absorb naturally occurring folic acid was estimated in two of the four patients (cases 3 and 4) by oral administration of yeast preparations containing an amount of conjugated folic acid comparable to the maximal amount present in a normal diet. (The total folic acid content of a general hospital diet was found to range from 1,000 to 1,500 µg daily.) The promptness of the reticulocyte responses in both indicates that an appreciable absorption of natural folic acid did occur. Indeed, subsequent administration of "deconjugated" natural folic acid and of synthetic folic acid

produced no further hematologic effect. It thus seems unlikely that a defect in folic acid absorption per se had led to the deficiency. Furthermore, there appeared to be no crucial inability in these patients to deconjugate naturally occurring folic acid conjugates, as was once postulated with respect to pernicious anemia.22, 28

The observed lack of increased urinary folic acid activity in cases 3 and 4 after prolonged oral administration of natural folic acid suggested that a severe tissue depletion existed. The sudden rise in urinary folic acid activity upon oral administration of synthetic folic acid (PGA) in both patients, however, might have been the result either of coincidental tissue saturation resulting from the immediately preceding therapy with natural folic acid, or of better absorption of the synthetic folic acid, or of both. It is to be noted that the ability of the normal subjects to absorb natural conjugated folic acid appeared to be limited to about 25%. Whereas deconjugation with chick pancreas conjugase raised the estimated absorption of folic acid to about 60%, this still fell short of the 95% absorption calculated for the synthetic preparation. The inefficiency with which the natural folic acid is absorbed is conceivably related to the existence of 30% of the folic acid activity, even after conjugase treatment, in a nondialyzable form. Since the urinary excretion of a mixture of deconjugated folic acid (yeast B) and synthetic folic acid approximated the estimated additive value of each if given separately, there appears to be no agent in yeast which inhibits the absorption of added PGA. Improvement of folic acid absorption following conjugase treatment, however, implies a limited ability to deconjugate natural folic acid within the bowel, and is possibly related in part to the presence of conjugase inhibitors in crude yeast.24,25 It appears probable that the abrupt rise in urinary folic acid activity which occurred in the two patients during the administration of synthetic folic acid came about as a result both of the better absorption of synthetic folic acid and of an impending tissue saturation with folic acid.

The folic acid excretion studies on normal subjects indicated that, when given subcutaneously, there was relatively little difference between single and thrice divided doses of folic acid. However, because the latter dosage schedule is theoretically more comparable for interpreting the absorption of folic acid from food or medication taken three times daily by mouth, only the data so obtained are depicted in figure 3, which indicates the relationship between the intake and the excretion of folic acid once a minimal dose is provided. The absence of an increase in urinary folic acid activity until doses of 200 µg or more of folic acid were administered daily has been observed by others.26 It is unlikely that this is a result of the insensitivity of the technic. Since fasting for three days does not reduce the urinary folic acid excretion in normal subjects,27 it is likely that this base line urinary excretion of folic acid represents an obligatory renal excretion of folic acid

which persists until tissue depletion has occurred.

The well known fact that many normal subjects do not excrete maximal amounts of folic acid on the first day of folic acid administration, although the appearance of administered folic acid in the urine is rapid, suggests either tissue unsaturation or an induced change in renal clearance. The likelihood that a partial folic acid unsaturation exists in normal persons receiving up to 1,500 µg of dietary folic acid activity daily is presumably related to the normally inefficient absorption of natural forms of folic acid.

The striking hematologic responses in cases 1 and 2 following the daily parenteral administration of 500 and 250 µg, respectively, of PGA, preclude an inability of these patients to utilize folic acid. Furthermore, the lack of response to subsequent equal doses of Leucovorin in case 1 suggests that no serious inefficiency in the conversion of PGA to CF existed as a result of cirrhosis. If the results of the studies of folic acid in normal subjects can be applied to cases 3 and 4, these patients each absorbed and responded to about 300 to 400 µg of folic acid daily while receiving yeast A. In a patient with macrocytic anemia and scurvy studied here, 125 µg daily produced a moderate reticulocyte response.19 It appears likely, then, that clinical folic acid deficiency may be alleviated by much smaller doses than are generally used, and that 200 to 300 µg of PGA daily probably constitutes adequate daily therapy for an adult. This being so, the folic acid absorbed from the diet may be sufficient to explain the reticulocyte responses in cases 3 and 4 during the preliminary control period, and emphasizes the need for minimizing the intake of folic acid-rich foods in planning adequately controlled studies of the megaloblastic anemias and for initiating preliminary control periods promptly after hospital admission.

Since the dietary intake of at least one of the four patients studied was not manifestly defective, and since no abnormalities of absorption of, responsiveness to, or excretion of folic acid were demonstrable, there remains the possibility of an abnormally high requirement for folic acid, perhaps coincident in three patients with a partial exogenous deficiency. It may be recalled that evidence of folic acid deficiency has failed to appear in young men whose diets were almost free of folic acid for as long as 18 months.28 In rats it is difficult to induce folic acid deficiency by simple exclusion of folic acid from the diet.20 In the puerperium, however, female rats on a folic acid-deficient diet are unable to lactate sufficiently to maintain their newborn, indicating an inability to support this added physiologic burden while on a limited intake of folic acid.29 There is at present no direct evidence of an increased requirement for folic acid in cirrhosis. However, the rapid rate of red cell turnover in patients with cirrhosis and anemia 11 may constitute such an increased demand. It is also conceivable that the heavy carbohydrate-derived caloric intake of the chronic alcoholic may induce a relative PGA deficiency analogous to the experimental choline deficiency produced in rats by Best and his associates by providing diets which contained large amounts of either ethanol or sucrose. 30

The findings in the 12 cirrhotic patients with macrocytic anemia in whose bone marrows there were present few abnormalities of red cell maturation and no abnormalities of granulocyte maturation, indicate that an aberration of PGA-CF metabolism is not involved in the usual patient with anemia of liver disease. Thus, all but one of six patients with normoblastic marrows studied excreted normal quantities of folic acid in the urine, and all six excreted administered PGA promptly. Most decisive is the fact that none of these patients responded hematologically to PGA or to CF. Moreover, it was observed that red cell survival was characteristically diminished in patients with cirrhosis, in proportion to the degree of anemia.11 Among them were four patients with megaloblastic marrows in whom abnormally short red cell survival persisted despite correction of the megaloblastosis with folic acid. Thus, the evidence indicates that the anemia of chronic liver disease is basically a hemolytic anemia, but that in certain instances a superimposed folic acid deficiency may exist.

The finding of adequate serum vitamin B₁₂ levels in all of these patients does not rule out the possibility that in other patients with cirrhosis an extrinsic vitamin B₁₂ dietary deficiency 8 or coincidental pernicious anemia may become the limiting factor in hematopoiesis. However, the observation of exceptionally high serum vitamin B₁₂ levels in cirrhotic patients who were subsisting on diets generally low in animal protein, reported here,11,16 is noteworthy. This high serum activity for Euglena gracilis does not appear to derive from the presence of growth-promoting substances other than vitamin B₁₂. Since the factors which normally govern vitamin B₁₂ levels in the serum are not understood, no clear explanation for this finding can be offered. It is conceivable that high vitamin B₁₂ levels may occur in the serum in the presence of a damaged liver as a result of impaired storage or utilization of vitamin B₁₂. Altered utilization associated with accumulation of vitamin B₁₂ in the serum might occur in conjunction with the impaired utilization of a closely associated metabolite, such as folic acid, as well as with impaired utilization of vitamin B₁₂ itself. Because suggestive evidence has been obtained that an increased intake of folic acid may lower the serum vitamin B₁₂ levels in monkeys, 31 and because administration of supplemental folic acid has been found to lower the serum B₁₂ levels of patients with pernicious anemia in remission, 32 a large dose of PGA (20 mg.) was given subcutaneously to each of three patients with hepatic cirrhosis and unusually high serum vitamin B₁₂ levels. No significant change in serum vitamin B₁₂ levels was detected at four or at 24 hours after administration of PGA; unfortunately, additional later determinations were not made. No correlation was noted between the serum vitamin B₁₂ levels and the hemoglobin levels in the patients presented here. None of the patients with megaloblastic anemia associated with folic acid deficiency had abnormally high serum vitamin B₁₂ levels. In addition, five patients studied here with macrocytic anemia of pregnancy due to folic acid deficiency had serum vitamin B_{12} levels in the normal range. It is unlikely, therefore, that the high vitamin B_{12} levels found in some patients with cirrhosis are related to a depletion of folic acid, and there is no hematologic evidence that faulty utilization of vitamin B_{12} existed in the patients studied with or without folic acid deficiency. A recent report by Jones and Mills ³³ suggests that abnormally high serum levels of vitamin B_{12} may be more prevalent in cirrhosis than our studies indicate, and that these levels are especially high in patients in liver coma.

The existence of "biochemical" scurvy in 11 of 16 patients, and of "clinical" scurvy in one, is probably not significant in the causation of macrocytic anemia in cirrhotics. Low or absent ascorbic acid in the peripheral blood buffy coat is common among patients from the economic and social groups from which these subjects came, with or without associated cirrhosis. The anomaly causing the rapid conversion of ascorbic acid to dehydroascorbic acid observed by Will and his associates ³⁴ in pernicious anemia may conceivably have further depressed ascorbic acid levels in these patients.

SUMMARY

Four of 16 patients with macrocytic anemia associated with hepatic cirrhosis and chronic alcoholism exhibited megaloblastic bone marrows. These four patients possessed normal serum vitamin B₁₂ levels but manifested a deficiency of folic acid by their subnormal daily urinary excretion of folic acid and of citrovorum factor, by their failure to excrete administered folic acid promptly, and by their striking clinical and hematologic responses to small daily doses of folic acid. The remaining 12 patients had "normoblastic" bone marrows, showed normal urinary levels of folic acid, and failed to respond to either synthetic folic acid or citrovorum factor. The dietary histories and alcoholic consumption of the cirrhotic patients with megaloblastic marrows were not significantly different from those of the group as a whole, and no abnormalities were apparent in these patients in the responsiveness to or in the absorption, deconjugation or renal excretion of folic acid. It is possible that an increased requirement for folic acid. compounded in most cases with marginal or inadequate dietary intakes, accounts for the apparent susceptibility of patients with chronic alcoholism and cirrhosis to the development of folic acid deficiency.

Comparative studies on normal subjects given an oral yeast preparation containing 1,500 µg of folic acid activity, largely in conjugated form, indicate that about 25% of this naturally occurring folic acid was absorbed. Preliminary deconjugation in vitro of the yeast folic acid conjugate increased the absorption to about 60% of the total orally administered folic acid activity. This was in contrast to the absorption of over 95% of synthetic folic acid (PGA) administered similarly. A folic acid dose-excretion curve was constructed for normal subjects given synthetic folic acid by injection in amounts ranging from 180 to 8,200 µg daily.

Serum vitamin B_{12} levels were within or above the normal range in 29 patients with cirrhosis, with or without anemia. Five patients had abnormally high serum vitamin B_{12} levels, but no relationship between the vitamin B_{12} level of the serum and the morphologic character of the blood or the apparent state of folic acid absorption or metabolism was apparent.

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SUMMARIO IN INTERLINGUA

Dece-sex patientes con anemia macrocytic associate con cirrhosis hepatic e alcoholismo chronic esseva studiate con respecto a lor metabolismo de acido folic, vitamina B_{12} , e acido ascorbic. In quatro de iste patientes le anemia esseva sever, e pronunciate anormalitates esseva evidente in le maturation del leucocytos e del erythrocytos con le resultato que le medulla ossee presentava le apparentia characteristic de arresto megaloblastic. Iste quatro patientes habeva libere acido hydrochloric in lor succo gastric e possedeva normal nivellos seral de vitamina B_{12} . Le existentia de un carentia de acido folic esseva indicate in iste patientes per lor subnormal nivellos urinari de acido folic e factor citrovorum, per lor excretion inadequate de doses exogene de acido folic, e per lor frappante e continue responsa clinic e hematologic a parve doses diurne de acido folic. Studios in duo de iste patientes indicava lor capacitate a ben responder a quantitates physiologic de levatura a contento de conjugate acido folic in administrationes oral. Nulle responsa occurreva post le administration subsequente de levatura a disconjugate acido folic o de synthetic acido folic.

Le remanente 12 patientes esseva minus severmente anemic e habeva "normoblastic" medullas ossee. Iste patientes excerneva normal quantitates de acido folic in lor urina e non respondeva a acido folic, a factor citrovorum, a acido ascorbic, o a ferro.

Le nivellos seral de vitamina B_{12} esseva intra o supra le limites normal in 29 patientes con cirrhosis, con o sin anemia. Cinque de iste patientes habeva anormalmente alte nivellos seral de vitamina B_{12} , sed nulle correlation esseva apparente, directe- o inversemente, inter le nivllo de vitamina B_{12} in le sero e le character morphologic del sanguine o le presentia del carentia de acido folic.

Le historias dietari e le consumption de alcohol del patientes cirrhotic con medullas megaloblastic non differeva significativemente ab illos del patientes cirrhotic con medullas normoblastic, e nulle anormalitate esseva apparente in le absorption o disconjugation de acido folic natural o in le responsa a acido folic synthetic. Il es possibile que un deficiente ingestion dietari de acido folic, combinate con un augmentate requirimento pro iste vitamina, explica le apparente susceptibilitate de patientes con alcoholismo chronic a disveloppar carentia de acido folic.

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A NEW CONCEPT OF FAMILIAL ADENOMATOSIS *

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THE disease familial adenomatosis has long been recognized, the first description being variously accredited to Menzel in 1721 and Virchow in 1863. It is characterized by a diffuse adenomatous involvement of the colon, a heredofamilial incidence and a close relationship to cancer of the large bowel. It is a distinct disease entity and is to be differentiated from postinflammatory polyposis and nonfamilial discrete polyps of the colon.

Multiple sessile or pedunculated proliferations of the mucous membrane of the entire colon are found. Often there is a predilection for the terminal bowel and, rarely, the involvement is segmental. The stomach and small bowel may occasionally be similarly involved.⁸ The polyps vary in size from a few millimeters in diameter to obstructing tumors, several centimeters in diameter. The proportion of sessile and pedunculated polyps can be correlated with the duration of the disease, the sessile polyps being noted during the early phase of the disease and the pedunculated type being seen later in the course of familial adenomatosis. The inheritable nature of the disease was originally observed by Cripps ⁴ in 1881, with his report of two patients, a brother, age 19, and a sister, age 17. Many subsequent papers have traced family pedigrees and established his observation as fact.

Although all of the genetic aspects of the disease are not completely clear, it is felt that the adenomatous proliferations of the intestinal mucosa represent a gene mutation. The altered gene is usually inherited as a nonsex-linked Mendelian dominant, and affects 50% of the succeeding generations. Since in one-half of the reported cases there has been a failure to demonstrate a familial history, the mutated gene nay also be transmitted as a recessive trait. Under the latter circumstances the hereditary factor in isolated cases of otherwise typical diffuse polyposis may not be recognized. The tendency of the polyps to undergo malignant changes has been long recognized, and constitutes the rationale for aggressive surgical treatment. A review of reported cases shows that most patients with familial adenomatosis will, if untreated, die of carcinoma of the colon before the age of 50.

In spite of an accumulation of considerable literature on the subject, our concepts of familial adenomatosis have changed little during the second quarter of this century. However, several recent articles have challenged the scope of the syndrome as classically described. Gardner, ^{5, 6, 7, 8} while studying a family group with intestinal polyposis, noted two additional and

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associated manifestations of abnormal growth. He called them, collectively, "surface tumors," and noted they were of a "hard" and a "soft" variety. The former were bony exostoses and the latter epidermoid cysts, fibromas or ill-defined masses of connective tissue. Six family members demonstrated all three manifestations of abnormal growth: polyps of the colon, exostoses and soft tissue growths. More than one type of soft lesion was usually seen in each patient. In several members of the family, surface tumors were noted prior to the recognition of the polyps of the colon, and in additional members of the family they were present in the absence of familial adenomatosis. Gardner felt that the polyposis and the associated growths were manifestations of a single dominant gene.

Oldfield ° recorded the occurrence of multiple polyps of the large bowel in three siblings of a family who suffered from sebocystomatosis. The three had undergone repeated operations for removal of cysts for many years prior to the establishment of the diagnosis of familial adenomatosis. The sebaceous cysts proved to be inherited as a Mendelian dominant and were of a paternal lineage. The author postulated that a second gene had undergone an associated and similar mutation in the three who developed polyposis.

O'Brien and Wels ¹⁰ described the synchronous occurrence of hereditary adenosis and benign fibrous tissue growths in six patients who underwent surgery for familial adenomatosis. In three patients postoperative fibromas developed at the operative sites. In case 1 two appeared at the ileostomy stoma; in case 2 a single fibroma developed at the operative scar, and in case 3 one was found in the abdominal wall and another in the mesentery. At the time of original surgery in cases 4 and 5, a retroperitoneal fibrous tissue tumor and a marked fibrous tissue hyperplasia, involving the mesentery, were seen. Two of his reported cases had associated single osteomas, and one had a fibrous tissue mass in the region of the right parotid gland.

Weiner and Cooper ¹¹ reported the occurrence of multiple polyposis of the colon, osteomatosis and soft tissue tumors in four brothers. In addition to the reports cited, an occasional reference in the earlier literature showed an association of soft tissue growth abnormalities and exostosis with familial adenomatosis. The number found in relation to the number of cases reviewed was few, and it is felt that the scarcity of such reports reflected the brevity of case abstracts and deletion of seemingly unrelated findings.

Miller and Sweet ¹² reported a case that was operated on again following extirpative surgery for familial adenomatosis. A tumor "the size of a hen's egg and located at the lower end of the original operative scar" was removed and microscopic study showed it to be a fibrosarcoma instead of the expected metastatic cancer. In case 2 of Pugh, ¹⁸ at the time of original surgery a large area of induration of the mesentery was noted, and on microscopic study it was found to be a mass of fibrous tissue. Guptill ¹⁴ commented on the presence of a nontender exostosis of the mandible in his case 1. Clark and Parker ¹⁶ noted in one of their patients with familial adenomatosis

three large retroperitoneal leiomyomas, all of which were found invading the mesentery of the small bowel. In addition, as one reads over the case reports of familial adenomatosis, there appears to be a disproportionate number of cases that develop postoperative intestinal obstruction secondary to formation of intra-abdominal fibrous bands.



Fig. 1. Case 1. Roentgenogram of skull, showing an osteoma of left frontal bone.

In view of the reports on the new concept of familial adenomatosis with the association of "hard and soft tissue tumors," three cases recently seen at Veterans Administration Hospital, Coral Gables, Florida, were evaluated in regard to the alleged association. Their case reports follow.

CASE REPORTS

Case 1. A 42 year old man presented a history of having multiple polyps of the colon, demonstrated while undergoing study for bleeding hemorrhoids in 1945. At that time a flat plate of the abdomen demonstrated a large mass. It was subsequently biopsied and a pathologic diagnosis of benign fibroma was made. The patient has been periodically seen at Veterans Administration Hospital, Coral Gables, Florida, since 1947. In view of the established diagnosis of familial adenomatosis, colectomy was recommended but was repeatedly deferred by the patient.

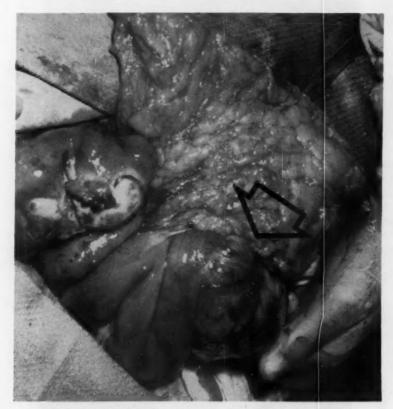


Fig. 2. Case 1. Operative photograph of two mesenteric fibromata.

Barium air-contrast roentgenograms showed polyps scattered throughout the colon. No gross evidence of malignancy of the colon or increase in size of the abdominal mass was noted during the period of observation. The patient always had the appearance of a well developed, well nourished white male. He usually appeared pale, and the findings of an abdominal mass, prolapsing hemorrhoids and polyps of the colon were repeatedly noted. The only other significant physical findings were a large osteoma, involving the right frontal bone (figure 1), noted prior to recog-

nition of the colonic polyps, and an osteoma, involving the right mandible, of a more recent appearance.

During one hospitalization a hemorrhoidectomy was performed. The operation was followed by a continuation of rectal bleeding, the patient's only gastrointestinal complaint. Multiple transfusions were periodically required. Following a severe episode of rectal bleeding a colectomy and ileosigmoidostomy were finally performed in August, 1952. At the time of surgery, in addition to the previously biopsied tumor, two mesenteric fibromas were seen, measuring 3 and 4 inches in diameter (figure 2).

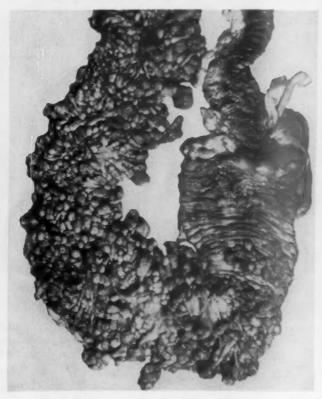


Fig. 3. Case 1. Resected colon, showing innumerable papillary tumors, ranging in size from 1 to 5 cm. in diameter.

The gross specimen of the colon showed the entire mucous membrane to be covered by innumerable papillary tumors, ranging in size from 1 to 5 cm. in diameter (figure 3). The cecum and distal portion of the descending colon were relatively free of polyps. A 25 cm. segment of the distal ileum was included, and one small 3 cm. sessile polyp was noted 8 cm. proximal to the valve. The small amount of mucous membrane present between the polyps was normal. No malignancy was noted. Postoperatively the polyps in the retained rectal segment were fulgurated,

and subsequently recurrent polyps have been removed during periodic proctoscopic examination.

In May, 1955, the patient was reëxplored surgically and the large abdominal mass which had been recognized for 10 years was removed (figure 4). It was found to measure 28 by 16 by 12 cm. and to weigh 4200 gm. (9.25 pounds). It lay in the space of Retzius and apparently originated from the periosteum of the symphysis pubis. The mass was reported as being a fibrosarcoma, grade II malignancy.

Since discharge the patient has remained free of any gastrointestinal or systemic complaints. He has two children, ages nine and 11, both of whom are currently



Fig. 4. Case 1. Large abdominal fibrosarcoma (9.25 pounds) removed at second operation.

being studied for polyposis of the colon. A firm nodule, having the gross characteristics of an osteoma, was noted on the vertex of the skull of the older child. The patient has no siblings. His father is living and well. His mother recently succumbed from a cancer of the bowel. She had undergone surgery and no polyps were seen at the time of surgery. No necropsy examination was performed. There is no additional knowledge of family illnesses or cause of death in other relatives.

Comment: This patient with familial adenomatosis had the associated lesions of osteomas, fibromas and fibrosarcoma. One osteoma was noted

prior to the recognition of the polyps, and at the time of recognition of the latter the fibrosarcoma had probably existed for a prolonged period, as suggested by the massive size of the tumor.

Case 2. A 21 year old man presented a history of onset of rectal bleeding two years prior to his present hospitalization. During the six months preceding admission bleeding had occurred daily, and the bowel movements had become loose and increased in number from two and three to 10 per day. There had been no associated pain or sense of urgency and no passage of mucus. The patient had noted a weight loss of 15 pounds and ease of fatigue, and his family had commented on his "ill appearance." He was evaluated by his physician, who detected anemia and multiple rectal polyps. Hospitalization was recommended. Of significance is the past history of his having had multiple operations between the ages of 12 and 20 years for the removal of numerous "growths under the skin."

On admission to the hospital the patient appeared well developed and well nourished. Abnormal physical findings were limited to a pallor of the skin and nucous membranes, multiple subcutaneous masses, and polyps on rectal examination. The subcutaneous masses numbered 16, and had the appearance of epidermoid cysts. Three polyps were felt on digital rectal examination, the largest measuring 4 cm. in diameter. No bony exostoses were detected. Numerous sessile and pedunculated polyps were seen on sigmoidoscopy. No site of ulceration or bleeding was noted.

The small amount of intervening mucous membrane appeared normal.

The patient had three siblings: a brother died during infancy of pneumonia; a second brother died from acute leukemia during early adolescence, and a third sibling, an 11 year old girl, is living and free of gastrointestinal complaints. She is currently being evaluated for the possible existence of polyposis of the colon. A maternal grandfather was known to have "cancer of the bowel." Knowledge regarding existence of associated polyposis is not available. The patient's mother has "nervous diarrhea" of five years' duration. Although movements are always loose and numerous, during times of nervous stress they increase to 10 a day. In view of the family history, the mother is suspected of having polyposis of the colon. Unfortunately, she has been recalcitrant to suggestions directed towards an adequate gastrointestinal investigation.

During his preliminary work-up a subcutaneous nodule was removed from the anterior chest wall and examined. The pathologic report revealed it to be an epidermal cyst. In view of the patient's youth and the feeling that he would coöperate with a program of adequate postoperative follow-up, an attempt was made to preserve the terminal rectum. After he had undergone a series of fulgurations of polyps of the terminal rectum, a colectomy with an ileosigmoidostomy was done. The operative and postoperative course was uncomplicated. The mucous membrane of the resected bowel was covered with a carpet of adenomatous proliferations (figure 5). No gross evidence of malignancy was detected. The microscopic study showed

"multiple adenomatous polyps with atypical epithelial changes."

Comment: This patient with familial adenomatosis had the associated lesions of multiple epidermoid cysts. Their existence and recognition had antedated the appearance of symptoms due to the polyposis by many years.

Case 3. A Negro male was first evaluated at the age of 54 years. At that time he presented a history of diarrhea of eight years' duration. The severity of the diarrhea had increased in the year preceding hospitalization, and the passage of loose stools was frequently accompanied by blood and mucus. Multiple polyps of the rectum and sigmoid were noted by both sigmoidoscopic and barium x-ray studies.



Fig. 5. Case 2. Air-contrast barium enema, showing polyposis of entire large bowel.

A laparotomy was performed during that hospitalization and an extensive induration of the mesentery of the sigmoid and rectosigmoid was noted. Biopsies were taken from several areas. In the belief that the induration represented malignant involvement, a colostomy was performed in preparation for an abdominoperineal resection. The histologic reports of the biopsied specimens revealed fibrous and lymphoid tissue with no malignant involvement.

In March, 1947, a second operation was undertaken with the intention of performing a left hemicolectomy. However, the extensive infiltrative process affixed

the colon to the bladder and pelvic walls in such a manner that the resection could not be carried below the sigmoid area. That part of the colon which was removed was found to be free of polyps. Because of the persistence of diarrhea and melena, the patient was reëvaluated in July, 1949, and at that time sigmoidoscopy again demonstrated polyposis, which was now described as multiple, ranging in size from 1 mm. to several centimeters in diameter. A third operation was done and the remaining sigmoid and rectum were removed. The pathology report described "myriads of firm papillary elevations with no evidence of malignancy." The patient did well postoperatively until April, 1951, when an episode of massive gastrointestinal



Fig. 6. Case 2. Resected colon, showing multiple adenomatous polyps.

bleeding occurred. Following multiple blood transfusions, an emergency operation was done and the source of hemorrhage was found to be a benign leiomyoma of the jejunum which measured 1 by 1.5 by 2 inches. Following the operation the patient has remained free of any gastrointestinal complaints.

Through his many hospitalizations, physical examinations repeatedly demonstrated the presence of multiple soft tissue tumors located in the subcutaneous tissue and involving most segments of the body. Their difference in size, shape and consistency suggested several different types of growth abnormalities. At various times several were removed and reports of epidermoid cysts and benign fibromas were made.

The soft tissue growths had apparently been present since childhood. Prior to establishment of the diagnosis of adenomatosis of the colon, believing the bleeding was of that etiology, the patient underwent a hemorrhoidectomy. He was unable to furnish a history regarding previous illnesses and present health of family members, due to limited contact, and family members were not available for examination.

Comment: This patient with a diagnosis of familial adenomatosis of a segmental type had had, since youth, the associated lesions of epidermoid cysts and subcutaneous fibromas. At the time of the initial operation the mesentery was found to be involved with an area of diffuse fibrosis. At a subsequent operation a leiomyoma of the small intestine was found.

DISCUSSION

The ideal approach to the management of cancer is one of prevention. That familial adenomatosis lends itself admirably to the practice of cancer prevention is attested to by the statement of Scarborough ¹⁶ that "probably no benign process has a higher incidence of malignant degeneration than polyposis." Familial adenomatosis begins as a benign process and develops into carcinoma of the large bowel if the patient survives long enough and the lesions are not detected and removed in their premalignant phase. In those so affected, the polyps characteristically undergo malignant changes at an early age, and the changes are often characterized by a multifocal malignant degeneration.

Because of the mildness of the early symptoms of the disease, the patients unfortunately do not present themselves for examination and treatment until a number of years have elapsed. The usual symptoms of diarrhea, passage of blood and mucus, and attacks of cramplike abdominal pain result in their being treated for prolonged periods for nonexistent hemorrhoids, colitis, amebiasis and other intestinal disorders. The correct diagnosis is finally established by an adequate investigation which includes digital rectal examination, sigmoidoscopy and roentgenographic study, the latter preferably by the combined double-contrast method. The frequency with which an invading malignant lesion is already present when the patient first applies for treatment is discouraging and approximates 40%. In many whose diagnoses are so delayed, palliative surgery alone is all that is practical. In a few the finding of associated malignancy does not necessarily exclude curative surgery, for in cancer of the bowel the relatively slow rate of growth and late metastasis serve to enhance the rate of operability.

A correct and early diagnosis can be made if a strong suspicion of polyposis is entertained and the appropriate studies are instituted in evaluation of suspicious gastrointestinal symptoms. When a rectal polyp is detected, a study for additional polyps is mandatory. When cancer of the colon is diagnosed a careful study for associated adenomas should be made. At the time of surgery this may be difficult for, in the absence of malignant changes, the external appearance of the bowel is usually normal, and since the polyps are often soft in consistency they frequently cannot be palpated through the bowel wall. If multiple polyps are detected and if they are of a noninflammatory type, a great responsibility is placed on the physician, for he must undertake an exhaustive study of relatives in order to detect the existence of polyps of the colon while still in a premalignant phase. The diagnosis cannot wait for establishment of a picture of large bowel dysfunction. That the relatives are apparently asymptomatic does not exclude the existence of polypoid disease.

Familial adenomatosis is considered to be a disease of adolescence and early adulthood, the average age for appearance of the polyps being 20 years. Although polyposis is usually manifest by the end of the third decade of life, youth or senility should not exclude a family member from an adequate investigation. Four children 17, 18, 19 were reported to have familial adenomatosis prior to two years of age, the youngest being a four month old infant. Of the eight patients that died in the series of McKenney, 20 four were 24 or under, the youngest being a 15 year old boy who developed a rectal perforation at the site of a necrosing carcinoma. The frequent need for examination of children arises from the fact that affected persons are usually well along in their reproductive life when the disease becomes clinically manifest. The average age at death is approximately 20 years younger than that from cancer of the rectum and colon in the general population. Death from malignant degeneration has occurred past the fifth decade, and Strode 21 reported the finding of familial adenomatosis in a patient aged 70.

To find a relative free of adenomas does not exclude him from further examination, as the adenomas may appear in subsequent years. A planned program of periodic reëxamination of all members of the family will afford a practical and rewarding means of preventing cancer. Lockhart-Mummery 22 examined a 39 year old man because of a family history of familial adenomatosis and found the colon free of polyps. On reëxamining the

patient four years later he detected "myriads of tiny polyps."

Any means by which attention is directed toward a case of familial adenomatosis will be welcome and will do much toward reducing the scourge of death attributed to that disease. That such a means might now be available is suggested by the reports and cases enumerated in this report. They suggest a correlation between the existence of exostoses, epidermoid

cysts and benign and malignant tumors of connective tissue origin and familial adenomatosis of the colon. The reports are still too few to permit more than a speculation as to whether the alleged association is significant. It is hoped that this report will result in a review of previous series of familial adenomatosis directed toward determining the coexistence of associated growth abnormalities. Comments on their presence or absence in future reports will be necessary. It cannot yet be said whether the abnormalities of growth represent additional manifestations of the same disease process caused by mutation of a single pleiotropic gene, or whether they are fortuitously occurring congenital anomalies due to multiple mutations of distinct genes.

An editorial 23 in The Lancet, commenting on the additional features associated with polyposis, states that "mutation of any of a group of distinct and linked genes may result in the same biochemical dysfunction. side effects of these mutations may well differ and so add different features

to the main condition."

An associated existence of multiple congenital anomalies is well known. Hereditary multiple exostosis is one of the most frequent hereditary malformations of the skeletal system. Sebocystomatosis represents another congenital malformation and both, in common with familial adenomatosis, develop gradually during and following childhood. All three are usually inherited as Mendelian dominant traits and are incompletely or nonsexlinked. All represent a disturbance of the normal growth patterns, the first two a disturbance of the glands of the colonic mucosa and skin, and the other, in common with tumors of connective tissue origin, a disturbance in growth of mesenchymal tissue.

From the reports enumerated from the literature, plus our own observation, it is suggested that patients with familial adenomatosis demonstrate an unusual mesenchymal tissue behavior. This may appear early and be manifest as fibromas, fibrosarcomas, leiomyomas or exostoses, frequently in subcutaneous, mesenteric or retroperitoneal locations. In other patients the abnormal tendency appears only in response to injury, and takes the form of intra-abdominal fibrous adhesions or connective tissue growths

at the sites of operative trauma.

It is suggested that, with the finding of one of the abovementioned growth abnormalities, a detailed personal and family history be obtained, directed toward detection of gastrointestinal symptoms. Even in their absence it is felt that a diagnostic survey should be undertaken to rule out the coexistence of familial adenomatosis. The finding of such growth abnormalities, in the absence of polyposis, might be suggestive of the inheritance of the abnormal gene, with the examination being performed in a stage prior to the appearance of colonic adenomatosis. Under such circumstances, the possible significance of the future appearance of gastrointestinal symptoms in the patient or his family should be made known.

CONCLUSION AND SUMMARY

Recent literature has suggested that there is an association between familial adenomatosis and additional growth abnormalities. Three cases of familial adenomatosis were recently seen and were evaluated in regard to the alleged association. In addition to the reported findings of epidermoid cysts, exostosis and fibromas, a fibrosarcoma and leiomyoma were detected. In all three of the cases reported, the existence of the associated growth abnormalities was recognized prior to the establishment of the diagnosis of familial adenomatosis or to the appearance of gastrointestinal symptoms.

If subsequent reports of additional cases of familial adenomatosis or reviews of previously reported series demonstrate the alleged association to be real, a means for early detection of premalignant polyps will be afforded. The finding of any of the reported abnormalities of growth will thus serve as an important tool in the practice of cancer prevention of the large intestine.

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SUMMARIO IN INTERLINGUA

Le morbo designate como adenomatosis familial es characterisate per un diffuse affection adenomatose del colon, un incidentia heredofamilial, e un stricte relation a cancere del grande intestino. Plure recente articulos ha attaccate le character restringite ascribite a iste syndrome in su description classic. Le association de altere anormalitates de crescentia con illo esseva signalate, incluse multiple cystes sebacee, crescentias de histo fibrose, e exostoses. Un revista del litteratura plus ancian revelava un certe numero de casos in que ille anormalitates de crescentia esseva associate con le lesiones polypoide de adenomatosis familial. In recente tempores le autores ha vidite tres casos de adenomatosis familial que illes ha evalutate in respecto al supramentionate association. A parte le coexistentia del jam enumerate lesiones, un del patientes habeva un fibrosarcoma e un altere un leiomyoma. In omne le tres casos. le existentia del associate anormalitates de crescentia esseva recognoscite ante le establimento del diagnose de adenomatosis familial e ante le apparition de symptomas

Le tactica ideal verso le problema de cancere visa a su prevention. Adenomatosis familial offere un campo admirabile pro le application de iste principio, viste le alte incidentia de degenerationes maligne in ille initialmente benigne processo. Omne medio resultante in le precoce signalation de adenomatosis familial es benvenite, nam omne tal medio contribue al reduction del mortalitate attribuibile a ille morbo. Le facto que un tal medio se trova nunc a nostre disposition es suggerite per le reportos e le casos enumerate in le presente articulo. Si futur reportos de casos additional de adenomatosis familial o revistas de series previemente publicate resulta in le verification del association in question, un medio additional pro le prevention de cancere del grande intestino va esser disponibile.

Post le constatation de un del supra-mentionate anormalitates de crescentia, le historia personal e familial del patiente debe esser obtenite con attention special prestate al detection de symptomas gastrointestinal. Mesmo in le absentia de tal symptomas nos crede recommendabile le execution de un revista diagnostic pro eliminar le possibilitate de coexistente adenomatosis familial.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(ELEVENTH RHEUMATISM REVIEW) *

Part II

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THE "COLLAGEN DISEASES"

THE practice of grouping together five or six probably unrelated diseases of unknown pathogenesis as "the collagen diseases" continued to disturb people. Sir Henry Cohen discussed the problem in detail both historically and critically in the light of our present knowledge. He pointed out that "the cliché—collagen disease—is becoming the refuge of the diagnostically destitute." 390 The editorial opinions expressed in the last Rheumatism Review concerning the use of this term remain valid, namely: "The term 'collagen diseases' serves a useful purpose at the present, but should be regarded as temporary, subject to revision as our knowledge advances." There were numerous reviews stressing the clinical features 712, 1086, 1117, 1463, 2298 and morphologic pathology 214, 596, 1117, 1187 of the group. Many of the latter reviews included detailed speculation on possible mechanisms, relying strongly on histochemical evidence. 214, 582, 594, 1187, 1463, 1755 Although not specific, fibrinoid change was regarded as the histologic hallmark and anatomic common denominator of this group of diseases. 1125, 2317 It was emphasized, however, that the capacity of connective tissue to respond to disease is limited,755 and that the unitarian concept of an all-embracing "rheumatic process" is no more reasonable than is the assumption that all diseases of the nervous system have a common etiology. 1125 The lack of agreement concerning the nature of the fibrinoid change remained unresolved, some feeling it represented altered ground substance, 1463, 1755, 1761 some raising the possibility of its intravascular origin. 1187 Alterations in the fine structure of collagen fibers, as revealed by the electron microscope, were demonstrated in experimentally produced local anaphylactic lesions of the Arthus type. 1745 [Most electron microscopic studies have not demonstrated such changes in collagen in the lesions of "collagen disease."—Ed.] A possible allergic basis was discussed critically.214 The relationship between connective tissue morphogenesis and the observed pathologic lesions was treated thoroughly. 1125, 1761

There were several case reports that could not be classified.¹⁵⁸⁵ One patient, presenting clinical features of polyarteritis and systemic lupus erythematosus (SLE), showed miliary tuberculosis at autopsy.¹¹⁰⁵ The interesting syndrome of cardio-vascular collagenosis was described in detail. In this entity, widespread focal involvement of the connective tissue was seen but no specific lesions of a particular member of the "collagen group" could be detected.¹³⁷ [It would be difficult to separate these patients from those with polyarteritis discussed below.—Ed.] The pulmonary manifestations of the various "collagen diseases" were believed to be strikingly similar.¹⁸³⁶ The ocular, ^{857, 996, 2050} and eye, ear, nose and throat ¹⁰³⁸ aspects of this group of diseases were reviewed. Many reviews were published concerning the treatment of the "collagen disease" group with cortisone or corticotropin. General principles were outlined in some.^{609, 1171, 1004} [Specific reports are discussed in their appropriate sections.—Ed.]

Systemic (Disseminated) Lupus Erythematosus

Since the term "disseminated" failed to distinguish between constitutional manifestations and widespread skin involvement without constitutional disturbances, it seemed preferable to designate the former condition as systemic lupus erythematosus.^{301, 913} The use of the L.E. cell test has broadened the concept of systemic lupus erythematosus (SLE) so that the unusual clinical onset and the extreme vagaries of the clinical course have been recognized.^{556, 918}

[It has also resulted in some confusion. Some workers have diagnosed SLE in any condition exhibiting the L-E phenomenon. Others have withheld judgment as to the specificity of this test.—Ed.] The relationship between discoid and systemic disease has not been entirely settled. Probably less than 1% of the patients with typical discoid lupus may develop systemic disease; however, as many as 25% of cases of SLE may have begun as the discoid form.³⁹¹ When thoroughly investigated, some patients with typical discoid lupus were found to have laboratory evidence of systemic disease, i.e., elevated erythrocyte sedimentation rate, elevated serum globulin and leukopenia, ^{391, 782} and positive L.E. cell preparations. ¹³⁷⁶

Clinical Features. Typical patients were females between 20 and 40 years of age, but the onset of disease could occur in either sex as early as three and as late as 63 years of age. 298, 782, 1081, 1613, 1801 The sex incidence was more nearly equal among a group of juvenile patients.782 The racial heritage was diverse and included Negroes. 718, 1295, 1800 Identical twin sisters 490 and a mother and son 1662 developed the disease, but hereditary factors have not been considered of major importance. Exposure to sunlight and drug therapy were common precipitating or exacerbating factors. 782, 1891 The effect of the pregnant state was not consistent, appearing to exacerbate the disease in two patients, 391 temporarily to benefit two patients, 539 but not to alter the course of three patients.⁵³⁹ The consensus of many dermatologists was that activity of the disease was not influenced by pregnancy. 606 [More factual data as to the effect of pregnancy on the course of this disease are needed .- Ed.] Major or minor surgical procedures were thought not to influence its course.833 Psychologic stress was said to be a consistent factor in the precipitation of onset, recurrence or exacerbation, whereas favorable psychologic influences appeared to mitigate the severity of the disease.275 [Observations were made on psychologic development, symptoms and clinical course of 42 patients, but unfortunately were presented only in abstract form. It would be of great interest to have more details of this provocative study. -Ed.] In one series more than 20% of the patients survived five years from clinical onset, 1081 and one additional patient survived 23 years from clinical onset.180

The protean clinical manifestations of SLE were again reported.^{87, 782, 1081, 1810, 1891} Specific aspects that were commented on included joint involvement that ranged from arthralgia to a deforming arthritis typical, by all examining modalities, of rheumatoid arthritis.²¹⁴⁷ Definite rheumatoid deformity was recorded in 19 of 62 patients with SLE.⁵⁵⁸ [In this series, the diagnosis of SLE often was made on the basis of a positive L.E. cell test. Most of us would regard many of these patients as having rheumatoid arthritis and exhibiting the L.E. phenomenon, rather than as having SLE.—Ed.] Polymorphous skin manifestations included urticaria tending to bulla formation,⁷⁷⁹ papulonecrotic tuberculid-like eruption,¹⁸⁸⁰ multiple skin and subcutaneous nodules,¹⁴⁷⁶ dermal gangrene ¹⁸⁸⁰ and Raynaud's syndrome.^{150, 550, 1880}

Nephropathy when present was usually of the nephrotic type, with initial proteinuria, and, later, hypoalbuminemia, edema and hypercholesterolemia. Azotemia and hypertension have been noted later in the course of the nephrotic syndrome. Renal manifestations were prominent at the clinical onset of the disease in one patient. Hypertension occurred only in association with severe renal involvement unless other factors were acting, but was infrequent with mild renal involvement. Hall Although evidence of cardiac involvement (pericardial, myocardial, endocardial) was common, no constant correlation between clinical findings and specific pathologic lesions was

noted. 556, 1002, 1891 Radiographic pulmonary changes consisting of small, irregular parenchymal shadows that varied in extent within short periods were seen in one third of a small group of patients.2127 [However, the changes described and illustrated were nonspecific and, without other clinical data, did not seem characteristic enough for diagnosis. -Ed.] Pulmonary manifestations, such as pneumonitis and pleuritis, have occasionally dominated the clinical picture. 1051 [Subsequently, the frequency of pulmonary parenchymal involvement has been emphasized by A. M. Harvey and coworkers.—Ed.]

Gastrointestinal symptoms occurred in approximately one third of 62 patients

in one series, and occasionally were a presenting complaint. 556 The frequency of splenomegaly has probably been overemphasized, since in recent groups not over 20% of patients have exhibited this finding. Lymphadenopathy was found in a little more than one third of the patients. 556, 1081 Multiple central nervous system manifestations, especially toxic psychosis and convulsive seizures, were seen during the active phase of the disease. 556, 1081 Epilepsy, however, has preceded by years the onset of recognized SLE.1822 Peripheral neuropathy 940 and spinal cord transection 1658 have been seen. With no gross mental or neurologic abnormalities, abnormal electro-encephalograms have been found. 1655 Cotton wool exudates, hemorrhages, retinal edema, papilledema and vasculitis were found on ocular fundus examination. 996, 1081 [Cytoid bodies were not emphasized, and it seems likely that their resemblance to exudates made it difficult to distinguish them clinically.—Ed.]

Platelet Thrombosis Syndrome. The platelet thrombosis syndrome (thrombotic micro-angiopathic hemolytic anemia, thrombotic micro-angiopathy) was thought to fall into the group of "collagen diseases" because of its frequent clinical similarity to SLE, polyarteritis and allied diseases; and because of pathologic evidence for the disseminated involvement of vessels of microscopic caliber. 146, 2093, 2095 Clinically this condition has been characterized by fever, hemolytic anemia, thrombocytopenia, purpura and fluctuating neurologic disturbances. The pathognomonic finding was a very widely disseminated thrombosis of the smallest caliber blood vessels, most often found in the myocardium, the capsular zone of the adrenals, and the renal cortex. The vessels were occluded by granular or hyaline eosinophilic material thought-but not proved—to be platelet thrombi.2093 Arthritic symptoms and findings were sometimes noted. Five new cases were reported. 146, 2008, 2005 Two patients with clinical and

autopsy findings very similar to SLE were described.146

Clinical Pathology. Moderate to severe degrees of normochromic, normocytic anemia were commonly seen, apparently due to retarded erythropoiesis without bone marrow hypoplasia or hemolysis. 555, 1055, 1208 The direct Coombs' test has been positive without evidence of hemolysis. 94, 418, 782 Cold autohemagglutinins have been demonstrated in sera of patients without evidence of hemolysis. 663, 782, 1845, 1865 Rare blood group antibodies have developed following whole blood transfusion. 1208, 1460 Leukopenia was a common finding, but a leukocyte response to infection or severe disease could occur.1460 Thrombocytopenic purpura has antedated by years other clinical evidence of SLE,782 and has occurred as well during the more typical clinical course. 413, 556, 713, 1891 A circulating anticoagulant retarding the conversion of prothrombin to thrombin has been noted to cause coagulation defects. 418 Serum globulin concentrations were commonly elevated, 556, 590, 1081, 1891 but serum albumin concentrations were not depressed in patients with clinically mild disease. 190 Complement activity of serum was often reduced. 605, 2186, 2215 Serum hexosamine levels were commonly elevated,208,209 but this was found in a variety of related and unrelated diseases.210 Chronic positive serologic tests for syphilis have been reported in patients with SLE without clinical or historical evidence of syphilis. 556, 1081, 1891, 2314 [And also have been shown to be negative with the treponema immobilization test.-Ed.] This so-called chronic biologic false-positive serologic test has preceded the clinical onset of SLE by years. 916, 1490

The "L.E. Cell." The typical L.E. cell was described as a large, mature polymorphonuclear neutrophilic leukocyte containing a mass of homogeneous, near-purple material (Wright's stain) displacing the nucleus to the periphery. 142, 890, 2045 Exact morphologic criteria were demanded in order to make a specific diagnosis. 107, 557, 890, 2821 The presence of the cell has been primarily an in vitro phenomenon; it has been demonstrated in the buffy coat smear of heparinized blood, 557, 1897, 2066, 2224 clotted blood, 228, 1261, 1262, 1359, 2321 defibrinated blood, 620, 1376 in smears of freshly drawn peripheral blood, 356a and in pericardial fluid. 1866 There was no agreement as to the most sensitive technic. Aggregates of polymorphonuclear neutrophilic leukocytes surrounding masses of homogeneous material (rosettes) were frequently found in association with L.E. cells, but their presence in a preparation was suggestive, not diagnostic. Atypical L.E. cells have been produced in artificial blisters on the skin of patients with SLE. 2208

Evidence was again presented that the inclusion material is partially depolymerized desoxyribose nucleic acid, primarily derived from nuclei of other polymorphonuclear granulocytes. An antigenically distinct serum factor found in the gamma globulin fraction was believed to cause the nucleolysis. ¹²⁶² The factor was associated, but not identical, with a plasma factor that reduced the redox activity of granulocytes; ³⁵⁴ cortisone did not inhibit its activity, ⁴³⁴ but cold did. ²⁰⁶⁶ It was not associated with serum desoxyribonuclease, ¹²¹⁶ but was inhibited by an inhibitor of serum DNAase obtained from human leukocytes; this suggested that the L.E. plasma factor alters the equilibrium of an intracellular system of DNAase and DNAase inhibitor. ¹²¹⁷

Rabbit antiserum against human granulocytes produced agglutination, lysis and nucleophagocytosis of normal leukocytes and formation of some cells that closely resembled L.E. cells. 651, 2822 A high molecular weight heparinoid was found, after incubation with normal gamma globulin, to induce the formation of L.E. cells. 1089 Fungi, particularly the aspergillus group, induced alterations in normal white blood cells closely resembling L.E. cells. 211 Other technics were less successful in producing L.E.-like cells. 1926

The L.E. cell phenomenon occurred in more than 60% of the patients with typical SLE. 557, 1262, 2066 It was considered a valuable diagnostic aid when the presenting features were atypical, 557, 912 but was of no prognostic import. 912, 1810, 2321 The L.E. cell phenomenon generally remained demonstrable in patients who had undergone a spontaneous remission, 294, 912, 1460 or who were maintained in asymptomatic remission with ACTH or cortisone. 294, 557, 1375, 1460, 1891, 1973, 2066 The L.E. phenomenon was reported in three patients with apparent penicillin sensitivity. 2186 [At least one of these patients had a clinical syndrome compatible with SLE.—Ed.] One L.E. cell was reported from a patient with generalized moniliasis. 785 [The cell, however, was not described, nor were photographs presented. More evidence is required before accepting this patient as a "bona fide" false-positive.—Ed.] L.E. cells have also been reported in the hydralazine syndrome. Many other patients with "collagen diseases" other than SLE, as well as a wide variety of unrelated diseases, did not demonstrate the phenomenon. 557, 909, 1262, 1810, 1078 [The occurrence of the L.E. phenomenon in patients with rheumatoid arthritis is discussed in the section on Rheumatoid Arthritis.—Ed.]

Etiology and Pathogenesis. The etiologic and pathogenetic basis for SLE continued to be highly speculative. 781, 1461, 1810 The apparent increase in incidence of SLE and other pararheumatic diseases suggested a relationship to the

widespread use of chemotherapeutic agents,⁷⁷⁸ as these agents may give rise to antigenically distinct gamma globulins that act as auto-antibodies.⁷⁸⁰ Histochemical studies supported the concept that a disturbance of nucleic acid metabolism is a pathogenetic factor.¹¹⁸⁶ Another suggested hypothesis referred to the production of an abnormal gamma globulin injurious to mesenchymal tissue.⁵⁹⁶ Viremia has been reported in one group of patients.¹⁴⁸⁶ [The last two sugges-

tions appear less tenable.-Ed.]

Pathology. The republication of the classic paper by Baehr, Klemperer and Schifrin,87 originally published in 1935, served to reëmphasize the widespread involvement of the peripheral vasculature. But no definite statement could be made concerning the relation between these lesions and the extravascular alterations in connective tissue such as fibrinoid change, swelling of the ground substance, fragmentation and destruction of elastic fibers, necrosis of tissue cells with nuclear pyknosis and karyorrhexis forming hematoxylin staining bodies. 299, 782, 1081, 1186, 1810, 2284 The earliest pathologic change, as exemplified in cutaneous blood vessels, was dilatation, followed by edema, exudation and infiltration of the vessel wall and abnormal staining of connective tissue with destruction of elastic fibers. 1461 However, these changes were not sufficiently specific for diagnostic purposes, 1081 although more advanced changes were considered diagnostic.²⁹⁹ In serial sections of muscles, nerves and synovia, this pattern of vascular alteration was seen typically in small veins with occasional lesions in small arteries, but perivascular cellular aggregations did occur without alteration of the vessel. Focal muscle and nerve degeneration could not be well correlated with the degree or distribution of the vascular damage. This vascular reaction was said to be identical with that seen in some patients with active rheumatoid arthritis. In comparison, the vascular lesion in arteritis was found primarily in small and medium-sized arteries, with occasional involvement of the veins, 1329, 1334

Examination of the eyes in one patient with retinopathy revealed "cytoid" bodies without necrotizing vasculitis, but some vessels were cuffed with lymphocytes. ¹⁵ Diffuse or focal fibrinous pericarditis frequently occurred, with fibrinoid change in the extracellular tissue. It healed at times with fibrous adhesions. ⁸⁸ Chronic intersitial pneumonitis, and alveolar hemorrhage plus basophilic mucinous edema of alveolar walls and peribronchial and perivascular tissues, were seen; these were distinguished from the changes of ordinary pyogenic bronchial pneumonia. ⁸⁸ Lesions of the alveolar septum and bronchiolar wall were reported in two patients without clinical evidence of pulmonary insufficiency. ¹²⁸⁶ Focal or disseminated encephalomalacia without clinical counterpart was attributed to an arteritis involving smaller cerebral arteries. ⁷⁶⁸ Certain lesions of the lymph nodes were felt to suggest the diagnosis. ¹⁵⁰³ Hematoxylin bodies were described in association with angiitis in the absence of other characteristic changes of SLE. ²²⁹¹ Synovial biopsies in four patients with SLE showed wide variations, ranging from mild inflammation to villous hyperplasia or scarring. ⁴⁵⁹

Treatment. The extreme vagaries of the clinical course of SLE make evaluation of therapy difficult. Prompt symptomatic improvement following administration of corticotropin and/or cortisone was repeatedly reported. 713, 1008, 1085, 1280, 1282, 1417, 1554, 1708, 2082, 2125, 2289 Large dosage of steroid was required to control symptoms in certain patients with extremely active disease. 915 There was no evidence that steroid therapy altered the fundamental disease process. 1269,

^{1460, 1891} Early mild nephropathies at times disappeared ⁵⁵⁸ or improved ¹⁹⁷³ with vigorous steroid therapy, but more advanced nephropathy usually was not benefited, or possibly was made worse. ^{928, 1058, 2147} Hemolytic anemia has been modified. ¹⁶⁶³ Serum hexosamine, ²⁰⁹ serum gamma globulin, ^{590, 2166} and plasma fibrinogen levels ²²⁷⁴ tended to fall, whereas serum complement titer ^{2166, 2215} and serum albumin ²²⁷⁴ rose with therapy. No relation was noted during hormonal therapy between changes in the erythrocyte sedimentation rate and any single electrophoretic fraction. ²²⁷⁴ Miliary tuberculosis has developed as a complication of corticosteroid therapy. ^{481, 807, 1086, 1184, 1892, 2179} [It also has occurred in patients with SLE who have not received steroids.—Ed.]

The distinct clinical impression has arisen in some quarters that the use of steroids in a severe exacerbation of SLE has been lifesaving and that therefore, necessarily, life has been prolonged.²⁹⁵, ³⁹¹, ¹⁰⁴⁷, ¹¹⁷¹, ¹⁹⁷³, ²¹⁴⁷ Evaluation of the effect of steroid therapy on the prolongation of life in a series of patients with SLE was attempted by two groups, but results were conflicting.⁵⁵⁸, ⁹¹³ [Each of these studies is subject to criticism of the experimental design. These two groups, alone, however, grappled with this difficult question. A more recent appraisal of the approach to this type of study has been made by A. M. Harvey and associates (Medicine 33: 291, 1954).—Ed.]

Other Measures. Atabrine administration coincided with periods of clinical improvement in one patient, 1599 but generally was found to have no salutary effect. 163, 1600 Temporary clinical remission occurred during chloramphenicol administration in one patient. 1018 Nitrogen mustard and triethylene melamine were administered to five patients, with inconsistent response. 1783 Administration of a cinchoninic acid derivative had no striking effect. 1736 Splenectomy did not consistently relieve throm-bocytopenic purpura when present, and did not appear to alter the course of patients without hematologic abnormalities. 1084 Hydrocortisone injected into the pleural space appeared to slow the rate of recurrence of effusion. 1085

Arteritis

The variety of conditions, both clinical and experimental, which are characterized by necrosis and inflammation of the arteries has become bewildering. While some proposed a classification based on type and distribution of lesions, 2312, 2313 the work of others suggested that such differences may depend primarily on the duration of the reaction. The following discussion, therefore, periarteritis nodosa, polyarteritis, panarteritis, necrotizing arteritis, allergic arteritis and hypersensitivity arteritis will be referred to simply as arteritis, to avoid implying etiologic and morphologic classifications not warranted at this time.

Clinical Features. There were several case reports illustrating that the syndrome occurred in infancy and childhood ^{9, 258, 504, 638} with the same manifestations as in adults. It is possible to cite only a few of the case reports and reviews that characterized the variegated clinical course of this disease and illustrated its protean nature.^{378, 875, 841, 956, 1100} Ocular lesions due to arteritis affecting extrinsic eye muscles, sclera and the uveal tract have been described.^{772, 1040, 1327, 2278} Skin involvement was manifested as gangrene,⁷⁵⁹ nodules,⁶¹⁷ and lesions of livedo racemosa.¹⁹⁴² Neuromuscular involvement without major arthritic manifestations was common, but Felty's syndrome (full-blown clinical rheumatoid arthritis) has been described with arterial lesions.^{1330, 1505} Arteritis

occurred without peripheral hypertension in a large group of patients.²²⁴⁷ Primary pulmonary hypertension with the characteristic lesions of pulmonary arteritis was described.2092 Bilateral involvement of the auditory nerve causing deafness was also reported.1430 Peripheral nerve symptoms were attributed to disease of the vasonervorem and simulated the Guillain-Barré syndrome. 1306 Renal lesions with characteristic necrotizing glomerulitis were seen, 1175 but uremia of a significant degree did not always indicate an early fatal outcome. 387 Unusual expressions of this disease included infarction of the liver, 1685, 1686 infarction of the ileum with perforation, 1057 and diabetes mellitus due to hemorrhagic pancreatic necrosis. 698 Cases with acquired hemolytic anemia were reported. 479, 1327 [These cases do not appear to be completely evaluated, and could well represent SLE.—Ed.] Arteritic lesions were also encountered in association with other diseases, such as tuberculous mediastinitis,761 disseminated platelet thrombosis, pulmonary silicotuberculosis and sarcoidosis-like lymphadenopathy.2001 [Although these reports are unusual, they add nothing to our understanding of the basic process. They do indicate that any vessel in the body may be involved and lead to symptoms.-Ed.]

Pathology. The pathologic lesion was described as an inflammation involving all layers of the vessel wall, usually with the deposition of fibrinoid material. The involvement in a vessel could be localized, with normal adjacent areas, and did not necessarily affect the entire circumference. The area of inflammation could be weakened, leading to an aneurysmal dilation, or the artery might thrombose, resulting in infarction of the tissue it supplied. All stages from acute to healed arterial lesions could be found in the same patient.

Arterial lesions were demonstrated in the synovia obtained by biopsy in two of four patients with periarteritis nodosa. An unusual granulomatous lesion of renal glomeruli was noted, 1429 and one additional case presented verrucous endocarditis at autopsy. In the variety that carried the eponym Wegener's disease, granulomatous lesions were found in the upper and lower respiratory tract as well as in the kidney, with typical arterial lesions elsewhere throughout the body. Moreover, with this represented a different entity because of the presence of these granulomata. So But others likened sarcoidosis to an arteritis, with the granulomatous lesions regarded as a stage of the disease process. 1054

Etiology. The etiology remained obscure, with both clinical and experimental observations continuing to emphasize the role of hypersensitivity in at least some forms of arteritis. Clinically, the administration of many medications has been associated with the development of arteritis: sulfonamides, 956 hydantoin, 685 penicillin, 212, 1361, 2211 a mercurial preparation, 707 and thiouracil. 109, 475, 956 [The association with thiouracil has always been reported in patients who were receiving or had recently received iodine.—Ed.] Arteritic lesions were reported in a patient with multiple myeloma receiving stilbamidine, 178 and in another case were attributed to bacterial hypersensitivity. 956 Löffler's syndrome, tropical eosinophilia, and periarteritis nodosa were considered [without concrete evidence—Ed.] to be gradations of a hyperergic vascular response. 517

Further studies on the pathogenesis of the lesions induced in rabbits by foreign protein injections were of potential significance. Particularly important was the demonstration that granulomatous lesions, in addition to vascular lesions, could be produced.^{742, 1748} The use of chemically homogeneous antigen made it possible to

determine the relationship of histologic lesions to the rate of disappearance of circulating antigen and the time of appearance of circulating antibody. All of the tissue lesions developed during the "immune" phase of antigen elimination, and regressed after all circulating antigen had been eliminated and free antibody had appeared in the circulation. The cardiac, vascular and renal alterations, as well as the granulomatous lesions, varied in morphologic characteristics according to the immunologic status at the time that the animals were sacrificed.742 The use of the ear chamber permitted in vivo observations of the earliest arteriolar alterations in rabbits receiving large doses of horse serum.577 Alterations in the distribution of body fluid were associated with the development of humoral antibody in rabbits injected intravenously with human serum, or fractions thereof; this was interpreted as indicating a defect in permeability of capillaries and of cell walls as a result of antigen-antibody union. 17, 18 Hypertension was not associated necessarily with experimentally produced arteritis. 1589 The addition of streptococcal products to the foreign protein used in producing these hypersensitive states was studied. 1496 Methods of producing arteritis, as well as cardiac and renal lesions, by sensitization were reviewed. 1192 Selye continued to regard arteritis as a "disease of adaptation." 1870 [The data supporting and criticizing this concept are reviewed in the section on The Adrenal Cortex and Rheumatic Diseases.-Ed.]

Many felt that confusion as to etiology was compounded by grouping several diseases under one heading. "The concept that all conditions in which there are vascular lesions characterized by fibrinoid necrosis and inflammatory reaction constitute one pathologic entity becomes untenable when the wide variety of experimental procedures that have given rise to the lesions in animals are considered, and when attention is focused upon the differences in morphology and distribution of the lesions in man" (Zeek ²³¹³). Classification based on type and distribution of the vascular lesions, including exact location of arterial or arteriolar involvement, subdivided "necrotizing angiitis" as follows: (a) classification periarteritis nodosa; (b) hypersensitivity angiitis; (c) angiitis of rheumatic fever; (d) allergic granulomatous angiitis; (e) temporal arteritis, and (f) other forms of arteritis. This classification was criticized for failing to take into account the varying nature of the histologic lesions according to the duration of the disease. 100

Laboratory Findings. Laboratory findings of a nonspecific nature, reflecting a systemic inflammatory process, were invariably present. But histologic study alone served to establish a diagnosis. Muscle biopsies were positive in 13% of 136 biopsies on 106 patients suspected clinically of having arteritis; results were positive in only 35% of biopsies from 26 patients subsequently proved to have the disease. Ninety-two per cent of the biopsies at random from clinically normal muscle were negative. Gobiously, a negative biopsy does not rule out the diagnosis.—Ed.] Urinary findings with the features of all phases of glomerulonephritis (red blood cells, oval fat bodies, fatty and waxy casts, broad casts and proteinuria) were reported as characteristic of arteritis, Total Republic Proteinuria and proteinuria.

Therapy. No curative therapy has been reported. Experimentally produced arterial lesions resulting from sensitivity to foreign protein have been suppressed with cortisone, corticotropin and salicylates. ^{156, 392, 745, 810, 1488} Clinically, numerous case reports have appeared of patients with arteritis treated with cortisone, hydrocortisone or corticotropin. ^{90, 595, 1271, 1363, 1378, 1515, 1703, 1905, 1931, 2094, 2096} The results have been beneficial in some for variable periods of time, depending on the length of the follow-up. Some have felt the hormones were

harmful and might initiate a more serious phase of the disease. ⁵⁹⁵ [Due to variations in the clinical course of this disease, it is impossible to ascribe harmful effects to these agents or to be sure of beneficial ones. There seems to be a much less predictable course following the administration of cortisone, hydrocortisone and corticotropin in arteritis than in rheumatoid arthritis or SLE.—Ed.] Reports of benefit attributed to the administration of para-aminosalicylic acid ³³¹ and para-aminobenzoic acid ¹⁴¹⁸ appeared.

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)

Progressive systemic sclerosis (PSS), a term suggested in 1945 by Goetz as more suitable than diffuse scleroderma to indicate the frequent visceral manifestations, was accepted by some ¹⁴⁷ [including the present reviewers.—Ed.]. Although many continued to use the term acrosclerosis to designate scleroderma associated with Raynaud's phenomenon as a separate entity, ^{839, 1304, 1714, 2142} evidence from a well-documented study failed to support this concept. ¹⁴⁷ [It is

suggested that the term acrosclerosis be abandoned.—Ed.]

Clinical Aspects. The disease frequently was first noticed because of pain, swelling and stiffness of the joints.¹⁴⁷ Clinical evidence of involvement of one or more viscera appeared in the majority of patients,^{147, 580, 1034, 1778} with a predilection for the esophagus, lungs,¹⁹¹⁰ heart ¹¹⁴ and kidneys.¹⁴⁸⁹ Pulmonary involvement was detected in five of 37 patients in one series; in four of these, scleroderma of the lungs had apparently preceded the development of cutaneous sclerosis.¹⁹¹⁰ The development of hypertension was considered unusual in association with untreated renal PSS.¹⁴⁸⁹ Paralytic ileus in an instance of widespread intestinal involvement led to death.¹⁶⁹⁰ [Whether ileus resulted from intrinsic intestinal lesions or the associated unexplained "plastic peritonitis" remains doubtful.—Ed.] Attention was called to the association of PSS with parotitis,³³⁹ rheumatoid arthritis,¹⁷¹⁴ rheumatic fever,¹⁷¹⁴ and Sjögren's syndrome.⁸⁹³ Nodular scleroderma was reported.¹⁸⁷⁶

The association of calcinosis with scleroderma was reëmphasized.^{209, 546, 1046} In a review of the literature on calcinosis, the author indicated that PSS has not been adequately excluded on histologic grounds in previous case report.²⁰⁹ [Thus, the estimated 30 to 40% incidence of PSS in patients with calcinosis may be too low.—Ed.]

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Laboratory Findings. As yet, no specific serologic tests for PSS have been devised. Abnormalities frequently encountered were elevated erythrocyte sedimentation rate, anemia, hypoalbuminemia and hyperglobulinemia.147, 682, 893, 1164 Low vital capacities were often recorded in patients with involvement of the chest wall and lungs.147 Electrocardiograms commonly revealed flattening or inversion of T waves, prolongation of QT intervals and depression of ST segments. 114, 147 In some patients, the absence of R waves in precordial leads suggested myocardial infarction.147 Frequent x-ray findings included nodular densities or linear streaks in the lung bases, with diffuse fibrosis, triangular contour of the heart and absence of peristalsis in the lower half of the esophagus. 147, 1084, 1910 Dilatation and absence of peristalsis in parts of the small intestine occurred, as well as stenosis of the cardia and pylorus.¹⁷⁷⁸ "Defective pharyngeal clearance" was demonstrated by cineradiographic studies of deglutition in patients with PSS, and the possible significance of these findings in regard to pulmonary complications was discussed.60 Resorption of the tufts of distal phalanges was noted in hand x-rays. 1046 A battery of tests performed on six patients with PSS was consistent with depressed adrenocortical function.1778 [The data are not impressive.—Ed.]

Pathology. By histologic examination, the lesions of PSS showed swelling and hyalinization of collagen bundles, and perivascular cuffing with lymphocytes and plasma cells, as well as intimal proliferation and medial thickening of small arteries. 147, 1489 Differentiation from dermatomyositis by histologic examination of skin and muscle biopsies continued to present difficulties. 48, 114

In one series, four of five autopsies revealed evidence of scleroderma in the endocardium, heart valves, pleura and pericardium.¹⁴⁷ In one patient with extensive sclerodermatous involvement of the intestinal tract, biliary obstruction resulted from swelling of the head of the pancreas; this organ contained arterial lesions.¹³⁴² Autopsies on three patients with scleroderma who died in uremia revealed vascular changes consistent with benign and malignant nephrosclerosis, and concentric intimal thickening of the intralobular arteries. The age of the sclerodermatous renal lesions was estimated to be between two to four weeks.¹⁴⁸⁹

Etiology. In PSS, as in many other chronic systemic diseases, correlations between emotional crises and the clinical course have been observed. 1428, 1510 [However, one author's belief 1510 that PSS is a manifestation and result of a psychosomatic disturbance appears to be based on insufficient evidence.—Ed.] It was postulated that PSS is associated with an antigen-antibody reaction within the walls of small arteries; whether the resulting manifestations are those of PSS or SLE might depend upon the severity, rapidity and localization of such reactions. 147 [Objective improvement following administration of hyaluronidase does not, contrary to the discussion in one report, 1673 indicate that a lack of hyaluronidase is an etiologic factor in scleroderma.—Ed.]

Treatment. In a series of nine patients, only one appeared to sustain symptomatic improvement during 30 months of cortisone therapy; only slight, transient benefit was observed in the other eight who received hormones for shorter periods.147 In a group of six patients, corticotropin or cortisone administration was associated with moderate temporary improvement in only two.630 In a third report, corticosteroid therapy in four patients was associated with temporary symptomatic improvement; but after a course of corticotropin or cortisone lasting 10 to 30 days, measurements of skin temperature, blood pressure and peripheral blood flow showed slight or no alteration from control levels, 968 In isolated case studies, or in general reviews of the treatment of "collagen diseases," the hormones, for the most part, were utilized for brief periods, symptomatic response was variable, and there was no evidence that this treatment affected the natural history of the disease. 268, 839, 874, 546, 682, 1342, 1363, 1554, 1708, 1887, ^{2032, 2108} During hormone administration, plasma gamma globulin and fibrinogen levels fell.2168 Although a cause-and-effect relationship could not be established, four patients died either during or immediately following hormone treatment. Predominant factors in the terminal illness of this group were serious infections, 339, 1164 hypertension with cerebrovascular hemorrhage, 129 and uremia. 1342, 1887

Experience with various other agents in the treatment of PSS was described. Of little or no demonstrable value were gold, arsenic, bismuth, iron, thyroid, stilbestrol, relaxin, testosterone, AT 10, glyceryl trinitrate ointment, Priscoline and alpha-tocopherol. 147, 630 Zarafonetis continued to recommend large doses (12 gm. daily or more) of para-aminobenzoic acid for six months or longer, and reported marked improvement in 16 and moderate improvement in 17 of a series of 40 patients. 2300 Others obtained objective improvement in only one of 14 patients given this dosage. 630 The use of large doses of para-aminobenzoic acid was not without

danger. It was pointed out that this drug may produce hypoglycemia, despite the fact that the increased amount of glucuronic acid excreted during its administration would give a positive reaction for glycosuria by the usual tests.²³¹⁰ Fatty changes in the heart, liver and kidney were found in humans and rabbits following PABA administration. Three deaths were attributed to its use as an antirheumatic agent.⁴⁵⁶ Improvement in the objective manifestations of PSS was reported to attend the administration of hyaluronidase by iontophoresis ¹⁶⁷⁸, ¹⁶⁷⁴ or by intramuscular injections.³⁶¹ Sympathectomy in selected patients was followed by reduction of Raynaud's phenomenon, loosening of skin and relief of dysphagia.⁶⁸⁰ [The occurrence of spontaneous remissions in early PSS demands cautious interpretation of apparent therapeutic success.—Ed.]

Dermatomyositis

The reports on dermatomyositis continued to be wholly descriptive. Many articles, in particular the "case report," defy comprehensive review. Frequently exact diagnostic criteria for dermatomyositis cannot be found in the protocols.²⁵⁴, 516, 1104, 1568, 1808, 1846, 2076, 2229

Clinical Features. In one series of 25 patients, the most common presenting symptom was a rash, with or without edema of the skin. 1890 Muscle aching and weakness were also frequent initial manifestations. In a given patient, however, the chief complaint might cover a wide spectrum, from ill-defined systemic symptoms such as loss of weight, 254 weakness, 2264 fatigue and lassitude, 675 and fever, 516 to a rash, 42, 1746 edema of the skin, 1388 or stiffness and pain of the skeletal musculature. 652 Raynaud's phenomenon was mentioned. 42, 675, 1890 Vesicular and bullous skin lesions, although unusual, caused confusion with other bullous diseases such as pemphigus and congenital porphyria. 652, 1890 Retinopathy in dermatomyositis was described. 516

Although striated muscle atrophy may be extensive, chronaxie testing showed no reaction of degeneration.^{297, 682, 2264} On the other hand, the mean duration of muscle action potential was reported as significantly decreased in patients with dermatomyositis as compared with normal subjects.²⁹⁷ Dysphagia was attributed in one instance to weakness of the soft palate, ¹³³⁸ and in another to loss of esophageal peristalsis. ¹³⁸⁸ Myasthenia gravis was suspected in one patient.⁹⁷⁵ In 24 cases of dermatomyositis with soft tissue calcification, the calcification was predominantly in tendons, skin, subcutaneous tissue and muscle. In rare instances, calcification was noted in the lungs and kidneys.²²³⁶

Pathology. No new features were reported. The microscopic picture of the skin remained as follows: hyperkeratosis or thinning of the epidermis, and diffuse low grade round cell infiltration of the subepithelial papillae with a few perivascular round cell infiltrates in the deeper corium. In muscle, findings were swelling and fragmentation of the fibers, nuclear proliferation of the sarcolemma, and some round cell infiltration; in advanced cases, fibrosis may obliterate the interstices and the muscle fibers. 975, 1338, 1746 An endarteritis of small arteries and arterioles was noted twice. 674, 1746 Collagen fibers, examined under the electron microscope, appeared normal in two cases with both dermatomyositis and scleroderma. 1875

Etiology. The cause of dermatomyositis remained unknown. The extraordinary association with malignant disease continued to receive special emphasis. 291, 439, 467, 674, 675, 1338, 1890, 1932 Although no comparative study on the general population was available, the association of the two conditions suggested a causal relationship because of the remissions of the dermatomyositis that follow treatment of the malignant lesion. In addition, dermatomyositis preceded the appearance of the malignant process by an average of 18.6 months. Paradoxically, in four out of five patients in whom a neoplasm progressed or metastasized after an initial good response to therapy, the dermatomyositis was not reactivated. The location and type of malignancy were diversified.⁴⁶⁷

Laboratory Findings. In the patients with the complication of calcinosis, the serum calcium, phosphorus and alkaline phosphatase were within normal limits.²²³⁶ Although creatinuria was observed, it was not helpful diagnostically and simply indicated striated muscle involvement.^{1890, 2076, 2229} Porphyrins were sought but not found. ^{602, 1388} [Biopsy of the skin and muscle remain the most helpful test, by simply confirming for the clinician that the patient has a nonsuppurative inflammatory disease.—Ed.]

Treatment. The management of dermatomyositis is palliative. 1654 There were a few reports on the use of corticotropin or cortisone. 1554, 1703, 1876, 2032 A patient was described as recovered and in complete remission after a 14-week follow-up. 2076 [But the case record could as well have described a penicillin reaction.—Ed.] Arrest of 18 months' duration without specific treatment was also recorded. 1654 One case progressed in spite of administration of cortisone and corticotropin. 1213 In one patient with dermatomyositis and calcinosis, the soft tissue calcification was stated to have disappeared after two ccurses of corticotropin. 269 Para-aminobenzoic acid was tried with success by some. 975, 2309

PSORIATIC ARTHRITIS

Opinion as to whether psoriatic arthritis constitutes a separate clinical entity continued to be divided. Among 6,814 patients admitted to a Copenhagen hospital, psoriasis was not associated with rheumatoid arthritis more frequently than with spondylitis, gout, muscular rheumatism or osteoarthritis. In 150 patients with psoriasis and rheumatoid arthritis, the clinical features were considered to correspond in general to those of rheumatoid arthritis without the skin disease. But Sherman described 15 patients with a type of arthritis peculiar to persons with psoriasis, which has a predilection for the distal joints of the hands and feet, with clinical and roentgenographic characteristics quite different from those of rheumatoid arthritis. Others agreed that "pure psoriatic arthritis" was an uncommon but distinctive entity involving the terminal interphalangeal joints. Such patients could, in addition, be afflicted with typical rheumatoid arthritis of other joints. In addition, be afflicted with

Clinical Features. All 15 patients in whom the disease was believed to be characteristic had major changes in the distal joints of the fingers or toes. In 13, psoriasis had been present for several years before arthritis appeared; in the other two, skin and joint involvement coincided. Joint involvement was occasionally sudden and acute in onset and, once established, tended to evolve in attacks with spontaneous remissions. The arthritis was asymmetric, and tended to be correlated with involvement of the nails. In seven additional patients, the psoriasis antedated the joint involvement by two to six years. The radiologic features of destruction of joint surfaces, with increased bone density rather than osteoporosis, were considered unlike those seen in rheumatoid arthritis. 1401, 2041

In 128 cases considered indistinguishable from rheumatoid arthritis, the psoriasis antedated the joint disease in 89. In only nine cases did the arthritis precede the skin involvement by a significant period of time. In 30 of the 128 cases the skin and joint manifestations appeared within a few weeks of each

other. There was no evident parallelism between the severity of cutaneous and of articular involvement. Any peripheral joints and any portion of the spine could be affected. Terminal interphalangeal joints were abnormal in 40% of the 112 most carefully studied cases. 2172 Of 107 patients with ankylos-

ing spondylitis, 2.7% were found to have psoriasis. 1785

Pathology. Material was obtained by biopsy or in the course of reconstructive surgery from 33 involved joints. In early lesions (two to eight weeks), the synovial membrane had the gross appearance of pale, edematous granulation tissue extending out from the joint and a few millimeters along the shaft of bone. At a somewhat later stage the synovium was thickened and injected, often eroding the articular margins but without pannus formation. Destruction of the adjacent bone accounted for the "gnawing away" of the shaft seen in roentgenograms. In late stages the joint was completely destroyed, with articulating ends of bone represented by cancellous stubs embedded in fibrous tissue which often surrounded the shaft of bone. Biopsies were performed on uninvolved joints in two patients with "typical psoriatic arthritis," and on normal knees in three patients with psoriasis uncomplicated by arthritis; no abnormalities were observed. The pathologic changes were not considered sufficiently specific to permit differentiation under the microscope. 1808, 2172

Etiology. Investigations of the families of 100 patients suggested that heredity might play a significant role. In 13% the family history disclosed psoriasis; in 12%, rheumatic disorders; and in 2%, both arthritis and psoriasis. 2172 Other factors suggested were chronic infection adjacent to the terminal interphalangeal joints, or asso-

ciated vascular changes.2041

Treatment. Both the skin and joint manifestations of psoriatic arthritis were observed to respond to corticotropin and cortisone. 854, 1678, 1898 Instances of lack of responsiveness of psoriasis to these hormones were noted, however. 1047 [The effect of these hormones in psoriatic arthritis does not appear to differ significantly from the experience in rheumatoid arthritis.—Ed.] Aminopterin (4-aminopteroyl glutamic acid) was observed to have favorable effects on both the skin and joint lesions when administered in doses of 1.5 to 2.0 mg. per day to 13 patients with psoriasis, six of whom had associated arthritis. Treatment was usually interrupted after 14 to 28 mg. had been given. Some degree of improvement resulted in all patients, with remissions lasting from two weeks to several months. Severe toxic reactions occurred in nearly all patients. 852 Cortisone was found to be more effective than Aminopterin in comparative trials. 852, 854

REITER'S SYNDROME

Several reviews of the literature concerning Reiter's syndrome and of the characteristics included in this diagnosis appeared.^{435, 855, 880, 1240, 1758} In general, only patients with the triad of urethritis, conjunctivitis and arthritis were included.

Clinical Data. As before, the syndrome usually was seen in young men, but its occurrence in one woman 1758 and in a boy of nine 485 was noted. Urethritis was usually the initial symptom, but occasionally arthritis or conjunctivitis appeared first.855, 880, 1240, 1802, 2251 The joint involvement was usually polyarticular, though arthritis of a single joint was reported.855 The clinical course was often prolonged, but usually resulted in complete recovery without residual damage. Permanent joint damage occurred in a few patients, 855, 880 persistent

deterioration of vision in another. 1802 In three patients the predominant manifestations were severe cystitis with hematuria. 1656

Skin lesions characteristic of keratodermia blennorrhagica and superficial ulcerations of the glans penis were noted. S55, 1240 Mucocutaneous lesions were present in all of 23 patients reported from a Veterans Administration hospital. In 18 the lesions were on the glans penis, 12 had lesions in the oral cavity, and five had keratodermia blennorrhagica. Conjunctivitis was the most common eye involvement, but corneal ulcerations and iritis were reported. S38, S80, 1240 Diarrhea was noted in only five of 23 patients. The hemagglutination titer with sensitized sheep cells was usually low. 2079

Etiology. No specific etiologic agent has been recognized. Some workers favored the thesis that pleuropneumonia-like organisms played a role in the disease. 1240, 1758 Pleuropneumonia-like organisms were found in the urethra of three patients, 1240, 2251 and in a fourth patient, positive cultures indicated a possible venereal transmission. 1848 Hall and Finegold found such organisms in only one of eight patients from whom urethral or prostatic exudate was cultured, but presented epidemiologic data suggesting that Reiter's syndrome may be a venereal disease. 880 [These organisms have been repeatedly recovered from the genitourinary tract in the absence of any detectable disease.—Ed.] Corner observed a boy in whom the serum agglutination titer for Shigella flexneri V rose to 1:480 during the active stage, and then returned to normal with subsidence of the disease. 435 Attempts to culture shigella from the stools were unsuccessful in five patients. 880

In reporting a patient with four attacks of keratodermia blennorrhagica, urethritis and arthritis, Auckland suggested, on the basis of histologic similarity, that the keratodermia was really psoriasis. Others agreed that this skin lesion cannot be differentiated from pustular psoriasis. The hypothesis that Reiter's syndrome represents one variant of the same tissue reaction pattern as rheumatoid arthritis was presented. 1802 [The fact that one patient developed a picture consistent with rheumatoid arthritis 13 years after his first attack of Reiter's syndrome offers little support for this thesis. Yet the possibility that the syndrome represents a variant of rheumatoid arthritis cannot be excluded.—Ed.]

Treatment. The consensus indicated that sulfonamides, penicillin, salicylates and Chloromycetin were of no value in this disease. 435, 855, 1240 In individual patients, there was some suggestion that improvement might have been related to Aureomycin, 838, 1843 to Terramycin 2251 and to dihydrostreptomycin. 855 Streptomycin appeared to be helpful in four of six patients, although the results were not dramatic.880 In patients with arthritis associated with urethritis, some concluded that treatment with antihistaminics was beneficial,974, 1281 [Since other treatment, often antibiotics, was given just before or at the time of the antihistaminic, the latter cannot be evaluated.-Ed.] ACTH was given to four patients. In all four there was a response, but three relapsed following withdrawal, and in one of these no improvement followed resumption of treatment. In one of the patients the ACTH was added to streptomycin therapy. Keratodermia blennorrhagica in a patient with rheumatoid spondylitis responded rapidly to treatment with ACTH. 1240 In another study, two of three patients receiving cortisone and one of three receiving ACTH experienced temporary incomplete remission of fever and arthritis.880 [In a syndrome in which the course is so varied and spontaneous remission occurs, interpretation of therapeutic results is extremely difficult. At present, no therapeutic agent has been shown to shorten the course of the disease.—Ed.]

NEUROTROPHIC ARTHROPATHY: CHARCOT'S JOINTS

Opinion as to the pathogenesis of joint changes accompanying lesions of the central nervous system continued to vary (Tenth Rheumatism Review). Therefore, the report of a case of progressive joint disorder apparently due solely to lack of protection given by the sense of pain is of particular interest. The patient, who from birth had shown consistent lack of appreciation of pain but had no neurologic abnormalities, developed lesions of the knee and spine at the age of 17, and of the hip at the age of 22. The changes in these joints were identical with those seen in Charcot's joints. 1645

Clinical Data. The neuropathic joints occurring as a complication of poorly controlled diabetes and diabetic neuropathy received the major attention; 32 additional cases were reported. 64, 146, 448, 658, 1191, 1382, 1010, 1017, 1896, 2224 In all of these patients the foot or ankle was involved. The most common site of fragmentation was the midtarsal joints, but destruction also was seen in the ankle joint 1191 and in the tarsal-metatarsal and metatarsal-phalangeal joints. The typical picture was one of progressive thickening of the foot without increased heat or fluid accumulation; irritability and discomfort were present, but not severe pain. 448 Some suggested that two factors may be operative in producing such destructive lesions of the bones of the feet: gradual dissolution of the tarsal bones and their articulations due to the diabetic neuropathy, and also rarefaction of the phalanges and metatarsals secondary to chronic infection in the adjacent soft tissues and arterial insufficiency. 145, 1617 Others felt that only the mechanical factors were important. 1382

Zucker and Marder described what is apparently the first report of a typical Charcot spine in a diabetic. The patient, a 47 year old woman, was known to have had severe and difficult-to-control diabetes for 14 years. Complicating this was a diabetic pseudotabetic neuropathy with absent deep reflexes, impaired vibratory and position sensation, Argyll Robertson pupils, and autonomic dysfunction of the urinary bladder. The etiologic and pathologic nature of the lesions was fully confirmed by complete postmortem examination. The spine showed a bony mass involving the second, third and fourth lumbar vertebrae, with compression of the vertebral bodies and destruction of the intervertebral discs. The right ankle also showed changes suggestive of Charcot's joint. 2824

Three additional cases of Charcot spine due to tabes dorsalis were reported, and the subject was reviewed. 984, 2116 In 22 patients with syringomyelia, seven had neurotrophic osteoarthropathy; in five patients the shoulder was affected, in two, one or both elbows. In the shoulder, the absorptive process predominated, and at times progressed very rapidly. 1939 Multiple joint involvement in the upper extremity due to syringomyelia was misdiagnosed as rheumatoid arthritis. 2110

Treatment. Treatment continued to be unsatisfactory. In the cases due to diabetes, treatment was directed at preventing or treating the neuropathy. In two patients with tarsal involvement, arrest of destructive changes was reported after lumbar sympathectomy; the cases were followed for 47 and 28 months, respectively. In a third case, lysis and absorption of bone proceeded steadily in spite of the performance of sympathectomy. Amputation was sometimes necessary. Fusion by intramedullary fixation was described as a method of treatment for an affected knee. However, the results recorded were not impressive.—Ed.]

HEMOPHILIC ARTHROPATHY

Seven cases with involvement of the hip were reviewed. The appearance varied according to the age at which the joint was affected. Before puberty the changes were similar to Legg-Perthes disease; after puberty, bone cyst formation and osteoarthritic changes were produced. Bleeding into bone as well as into the joint was believed to be important in producing these alterations.²²⁶⁹ Discoloration of the synovial membrane due to loading of the synovial cells with hemosiderin resulted from repeated hemarthroses in hemophilia as well as other conditions. In hemochromatosis, this pigment was confined to the surface layers of the synovium. There was no evidence of reaction to the presence of this pigment in the synovial cells.⁴⁰⁸

Quick recommended treatment of fresh intra-articular bleeding by cold, pressure and rest, as well as measures to correct the coagulation defect. In addition to these measures, MacAusland and Gartland attempted to hasten absorption of blood from the synovial cavity by aspiration and intra-articular injection of hyaluronidase. Results were considered good in 11 of 13 joints so treated. After the clotting time has been returned to normal, equally good results are obtained from aspiration alone.—Ed.] Reluctance to undertake rehabilitation of hemophiliacs with severe joint contractures for fear of precipitating grave hemorrhage was noted. However, the feasibility of correcting deformities by traction and physical therapy, using gentle methods, was demonstrated in one patient.

RHEUMATIC (HENOCH-SCHOENLEIN) PURPURA

This form of purpura, associated with an erythematous skin lesion and gastro-intestinal and joint manifestations, is conventionally classified with the allergic purpuras. "But in fact, apart from a very small proportion of cases which are undoubtedly due to hypersensitivity to foods, the cause of the syndrome is unknown and its allergic basis is entirely unproved" (Ackroyd 4). The clinical features were reviewed, and 58 additional cases of the disease were reported. 510, 1260, 1278, 1279, 1659, 2288 Joint involvement was described as transitory, usually polyarticular and sometimes migratory. Arthralgia, often associated with diffuse pain in the limbs, occurred with or without periarticular swelling and tenderness; clinically detectable effusions into the joint were considered rare. In one series of 35 patients, 20 had joint symptoms. 510 Nephritis was at times a complication, 1279 and the difficulty in differentiating this disease from arteritis and systemic lupus erythematosus was noted. 510, 1278

Histologic studies of the purpuric lesions before, during and after corticotropin therapy were reported. The premedication "early lesion" showed intense subacute angiitis of the upper corium with mononuclear and polymorphonuclear leukocytic infiltration, capillary rhexis and segmental vascular necrosis. Biopsies taken during therapy were essentially unchanged. A biopsy taken 17 days after cessation of therapy showed almost complete reversal of the findings. 1278 Two courses of corticotropin were given to one patient, with remission after the second course. It was felt that the hormone may have inhibited the development of new inflammatory skin lesions but that it did not affect the regression of existing lesions. 1278 In another patient corticotropin was thought to have had no effect on the course of the disease. 2288

ALKAPTONURIA, OCHRONOSIS AND OCHRONOTIC ARTHRITIS

The subject of alkaptonuria was reviewed 720, 1407 and 19 new cases were reported. 110, 187, 424, 720, 808, 1252, 1402, 1407, 1709, 1826, 1889, 2259 For the most part, they were typical of the patients previously described and added little to the known clinical characteristics of the disease. Most of the patients had been aware of discolored urine since early childhood. In three patients, an increase in the darkness of the urine was noted during periods of excitement and following the ingestion of mustard. It was again emphasized that scleral pigmentation has not been seen in a person under the age of 23. 1467 In the first report of a case with polycythemia vera, the association was felt to be a chance occurrence. The syndrome was also seen with glomerulonephritis and purpura. The benign nature of the disease was underscored by a report of death from other causes in a patient at the age of 99.720 The disease appeared to be seen more frequently. The first case from Africa was reported, 1826 as well as the first found in an Australian native. 2259

Heredity. It was again pointed out that this disease is the best example of a metabolic defect occurring in accordance with mendelian law, in that 42% of the reported patients had consanguineous parents, usually cousins. It occurred in three siblings whose parents were second cousins. Alkaptonuria was present in three of nine children of an alkaptonuric father and an apparently normal mother. Four of these offspring had children and, of these, one who himself did not have alkaptonuria sired two alkaptonurics out of four births. His wife was his maternal first cousin. 1467

Laboratory Findings. The usual clinical methods for the identification of homogentisic acid in the urine were discussed. T20, 1252, 1820 A more specific method was described, using paper chromatography, treatment with phosphomolybdate, and measurement of absorption in the ultraviolet spectrum. Studies on the oxidation of homogentisic acid in urine using this method showed that it was converted to its quinone in the presence of nitrous acid or when the urine was made alkaline. Paper chromatography of the amino acids of the urine and electrophoretic analysis of the plasma proteins were normal in one case of alkaptonuria. 808

Recognized x-ray findings in ochronotic arthritis were again described. 187, 720, 1467, 1826 Excellent examples of spine involvement were presented, showing the characteristic, thin, densely calcified intervertebral discs, with fraying and spurring of the adjoining vertebral bodies. In addition, there were degenerative osteoarthritic changes in the lumbosacral and sacroiliac spine, shoulder, hip and knee joints. 720, 1826 In one patient, osteoarthritic changes in the spine preceded by three years the appear-

ance of calcification of the intervertebral discs.187

Pathology. At operation for repair of a tear in the medial semilunar cartilage of the knee, the articular cartilage was found to be greenish black; synovial villi were hypertrophied and bluish black. The cruciate ligaments were slightly tinted and the joint capsule was normal in color. On microscopic examination, the cartilage was fragmented, degenerated and diffusely pigmented. Lymphocytes and plasma cells were present in abundance. An excellent description of the postmortem findings in two patients was given. Black pigment was found in the costal cartilages, cartilages of the sternoclavicular joints, laryngeal, thyroid, tracheal and bronchial cartilages, intervertebral discs, mitral valve ring, endocardium, chordae tendineae, bronchial cartilages and meninges. Black punctate spots were found in the kidney, and the prostate contained black gritty concretions.

Etiology and Pathogenesis. Well controlled metabolic studies in alkaptonuric patients confirmed the previous observation that homogentisic acid excretion varied

directly with the dietary protein intake, and that 1-phenylalanine, the natural form, was converted to homogentisic acid more rapidly and to a greater extent than d-phenylalanine. Various substances which may have an effect on enzyme systems or carbohydrate metabolism, mainly vitamins A, B, C, D, K_1 , insulin, adrenocortical extract, liver extract and tyrosinase, had no effect on the excretion of homogentisic acid. [Corticosteroids were not tested.—Ed.] Brewer's yeast increased homogentisic acid excretion, but this was thought to be due to the high protein content. It was suggested that experimentally induced alkaptonuria is due to the overloading of an enzyme system for which ascorbic acid is essential. 720

Treatment. In two patients treated with cortisone, the joint symptoms responded dramatically to doses of 100 to 300 mg. daily. When dosage was lowered to 50 mg. a day, symptoms returned. The colored matter disappeared from the urine during treatment and reappeared when therapy was stopped. No metabolic studies were performed.^{187, 424} In a third patient, arthritis was relieved but the urinary abnormality persisted.²⁰⁷⁵ Corticotropin in doses of 40 to 80 mg. per day afforded no benefit in one patient.¹⁸⁷

THE JOINTS IN ACROMEGALY

An excellent clinical, pathologic, and chemical description of the articular changes in acromegaly was based on a study of 25 patients (Kellgren, Ball and Tutton 1127). Sixteen of the patients had some arthritic complaints and three had crippling involvement. Fingers were most often involved, but the back, knees, hips, wrists and elbows were occasionally affected. Stiffness was notably absent. Enlargement of the joints was noted in all patients. Many of them had increased mobility of the extremities, but in four motion was restricted. Radiologic findings included hypertrophic changes in the spine and costochondral junctions, and tufting of the terminal phalanges. The most characteristic roent-gen finding was an increase in joint space, reflecting the thickening of articular cartilage and soft tissues. Bilateral median nerve lesions at the wrist due to compression were found in three patients; in one patient this was relieved by exploration of the carpal tunnel. [The clinical similarity of this finding to the involvement of the carpal canal in amyloidosis should be noted.—Ed.]

Histologic examination of joints showed increased cartilage thickness and overgrowth and fibrous thickening of the soft tissues, but no evidence of inflammation. The thickened cartilage showed various types of degenerative changes, some of which differed from those of usual degenerative joint disease. On the basis of histologic evidence (including specific staining and the electron microscopic picture of collagen), it was believed that acromegalic connective tissue was qualitatively normal, although increased in amount. Procollagen was not abnormal. Acromegalic muscle contained 10% more collagen than did normal muscle, but did not differ qualitatively from normal muscle. The difference between normal and acromegalic skin in water, collagen and fat content appeared to be quantitative rather than qualitative. The action of hyaluronidase injected subcutaneously appeared to be decreased in patients with acromegaly. 1127

PALINDROMIC RHEUMATISM

A few additional cases of palindromic rheumatism were described. 494, 1297, 2201, 2315 Psychiatric investigation of a patient with this syndrome disclosed correlation of the attacks with emotional stress. 2315 Corticotropin was observed to accelerate the return of the joints to normal in one patient. 494

PHARMACEUTIC ARTHRITIS AND ARTHRALGIA

Hydralazine Reaction. A syndrome closely resembling rheumatoid arthritis was observed in patients receiving hydralazine (Apresoline) for treatment of hypertension. This appeared after several months of drug administration and differed from the usual type of hypersensitivity reaction. Discontinuation of the drug was followed by restoration of the joints to normal. [Subsequent to the period covered by this Review, this clinical syndrome has been more adequately defined. Manifestations simulating systemic lupus erythematosus, including the demonstration of the L. E. cell phenomenon, have been noted.—Ed.]

Serum Sickness Type of Reactions. In rare cases of serum sickness, the joint symptoms were observed to persist as long as three or four months after other manifestations had subsided.²¹² This type of reaction to penicillin was difficult to recognize in patients who did not develop urticaria or other skin lesions.¹⁶²⁹ Sodium dehydrocholate by intravenous injection was used with good effect in serum sickness type of penicillin reactions.¹⁶²⁹

OTHER TYPES OF ARTHRITIS

Several conditions treated as clinical entities in previous reviews are conspicuous by their absence from the recent literature. "Allergic arthritis," "endocrine" or "menopausal" arthritis, and "metabolic" arthritis are terms which seem to be disappearing. Intermittent hydrarthrosis received only passing mention. 1297

Periodic arthralgia in 23 patients in five generations of a family was reported, but this did not appear to be a well defined entity. The occurrence of hemorrhagic spots in some of the patients raised the question of classifying these diseases in the rheumatic (Henoch-Schoenlein) purpura group.¹⁷³³

Transient synovitis of the hip joints in 13 children was characterized by an unexplained onset of pain in the hip and limping, with few or no objective findings. This was a benign condition, its importance lying in differentiation from other, more severe hip disease. Treatment was symptomatic and conservative, although leg traction was used in some instances. This, too, was a rather poorly defined entity, and only a short follow-up was possible. It was suggested that this disease was due to an "allergic hypersensitivity," or to a focal infection. [Convincing evidence was not given.—Ed.]

In a review of Whipple's intestinal lipodystrophy, four new patients were combined with 22 previously reported. On the basis of the frequent presence of arthritis and the many manifestations of generalized disease apart from the gastrointestinal system (lymphadenopathy, pathologic findings of panserositis, and inflammatory vascular lesions), it was suggested that this entity should be included as another manifestation of the diseases of the "rheumatic state." 1843

THE PAINFUL SHOULDER

Study of those conditions whose chief symptom is pain in the shoulder continued to be hampered by lack of uniformity in terminology. Most laymen consider every painful shoulder to be "bursitis"; many physicians are no more accurate. 446, 1850, 1423 Primary subacromial bursitis per se does not exist; involvement of this structure is a sequel to some other lesion, most often calcareous tendinitis according to DePalma, who has carried out extensive dissections in many

shoulders.⁵⁰⁸ The persistence of the term reflects the vagueness of diagnostic effort; ¹⁷⁹¹ nevertheless, it is the one still most commonly employed.²²⁷⁶ Other terms used for one situation or another in the shoulder include "Duplay's disease," "frozen shoulder," "scapulohumeral arthritis," "adhesive capsulitis," "periarticular fibrositis," "myositis," "peritendinitis" and "periarthritis." ¹⁷⁷¹ But despite confusion in terminology and etiology, considerable progress has been made in separating the various entities grouped under this heading.⁵⁰⁵

Anatomy. Any understanding of the "shoulder syndrome" (a term suggested as a substitute for the usual designation of "painful shoulder" ^{1568, 2029}) must be preceded by a knowledge of the anatomy and functional physiology of the joint, for the shoulder appears to be inadequately adapted from an evolutionary standpoint to meet the demands of a prehensile extremity. ^{492, 505, 508, 1950}

The capsule of the shoulder is a loose, redundant structure permitting the unusual motility which the joint exhibits. In its superior portion it is reinforced by the conjoined tendons of the rotator muscles: the supraspinatus, infraspinatus, and teres minor attaching to the greater tuberosity and acting as external rotators, and the subscapularis attaching to the lesser tuberosity passes under the acromial process with very little clearance. Intimately related to this capsule is the deltoid muscle, forming an outer muscular sleeve, and the long head of the biceps brachii gliding in its special sheath through the bicipital groove. This tendon and tendon sheath actually form a prolongation of the shoulder joint, with the synovial membrane closing almost two inches below the joint proper. When the arm is passively elevated, only about one-half inch of tendon remains within the joint; when the arm is depressed and externally rotated, almost two inches of the tendon are intra-articular. 508, 509, 1300, 1368

Pathogenesis of Shoulder Pain. DePalma, Collery and Bennet studied 108 cadaver shoulders (12 from fetuses and 96 from cadavers ranging in age from 14 to 87 years), and concluded that progressive degenerative changes occur in the articular cartilage of the glenoid cavity and the glenoidal labrum from the second decade of life, and in the biceps tendon and rotator cuff tendon from the fifth decade. Solve However, rather prominent degenerative changes did not appear to be incompatible with good function. Solve In a study of the detailed anatomy of the rotator cuff and related structures in 106 shoulder joints from subjects whose clinical history and status were known, Olsson found no association between degenerative changes of various types and a history of previous or active shoulder pain. He also studied possible associated factors in 147 patients with shoulder pain in comparison with 522 patients with no history of such complaint. The frequency of shoulder pain showed no correlation with amount of physical work, with thyroid disease or with diabetes. Cardiac disease appeared to predispose to shoulder pain, but this was attributed to disuse. Recumbency in bed gave rise to this symptom more frequently than did trauma. 1583

One of the most intriguing papers of the period was a study of "Life Stress, Emotions, and Painful Stiff Shoulder," by Lorenz and Musser. Their concluding suggestion, "that the psychosomatic approach be added to the other fields of specialized knowledge," should be heeded by all physicians treating patients with shoulder pain.

"Calcific Tendinitis." The most clearly defined painful shoulder condition, and the one on which there appeared to be rather general agreement, is that associated with single or multiple isolated deposits of calcium in the musculotendinous cuff. Because of this, the terms "calcific (or calcareous) tendinitis," "tendinitis" or "peritendinitis," either singly or in combination, were popular, 160, 446, 502, 803, 1188, 1698, 1791, 2060, 2276 although some writers continued to specify "bursi-

tis" alone. 144, 658, 714, 725, 1365, 1584, 1588, 1598, 1602, 1626, 2026, 2036. One author suggested the term "tendinosis," in view of the fact that degenerative disease is the underlying pathologic change. 174 An excellent description of the gross and microscopic appearance of lesions found in the rotator cuff was presented by Pedersen and Key 1626 on the basis of material removed at operation on 55 patients for "subdeltoid bursitis with calcification." This study tended to support the theory that the underlying pathology is one of degeneration in the tendon, with subsequent deposition of calcium in necrotic tissues and an ensuing secondary inflam-

matory reaction.

Clinical Data. The patient is most commonly observed in an acute phase, usually characterized by abrupt onset of severe pain in the region of the shoulder, with radiation down the arm. The arm is held tight to the side and attempts by the examiner to rotate or elevate the arm are met with sharp resistance on the part of the patient because of pain. There is marked tenderness, localized to a point somewhere over the upper and outer aspect of the shoulder. Following treatment (and often, indeed, without treatment), the acute phase passes into a subacute or chronic stage, with or without subsequent acute exacerbations. 174, 446, 505, 1698, 1763, 2276 Opinion was divided as to the sex incidence, some writers claiming a predominance in males, 447, 505, 1568, 1763 others in females, 658, 1950 and one noting no significant difference.1740 Although the fourth and fifth decades of life are usually claimed to be the time of greatest occurrence, 505, 1950 one author 1740 cited Bosworth's study of 6,061 persons, of whom 165 (2.6%) showed calcifications, and pointed out that almost 90% were under 40 years of age. [This paper was reviewed in the Ninth Rheumatism Review .- Ed.] X-ray of the shoulder showed one or more deposits of calcium in the rotator tendon cuff, usually in the supraspinatus tendon, of sizes varying from a pinhead to several centimeters. 144. 174, 447, 502, 658, 1850, 1593, 1602, 1698, 1768, 2169, 2276 In an unusual case the calcium deposit was so extensive as to penetrate into the humerus itself.1183 For proper visualization, two views of the shoulder should be taken, one in external rotation, one in internal rotation. 1350, 1365, 1593, 2276 But a negative x-ray does not rule out the diagnosis, since many early soft calcifications are not visible. 1626, 1763

Treatment. Roentgen therapy for the acute symptoms was again advocated by the majority of writers. 144, 174, 446, 502, 658, 725, 1078, 1365, 1802, 2276 However, Plenk obtained no better results in 11 acute and 10 chronic cases who actually received roentgen therapy than were seen in 10 acute and seven chronic cases who were placed in the x-ray machine but shielded from irradiation. 1666 Such controlled

studies are desirable in a larger series of patients.—Ed.]

ACTH and cortisone, although not recommended for routine use, have at times produced spectacular results. Ti4, 1698, 2026, 2029, 2030, 2032 [Spectacular results also occur, occasionally, without any specific treatment.—Ed.] Phenylbutazone produced either complete remission or marked improvement in 17 of 20 cases treated by Strazza and Ressetar, 2080 and major improvement in 67% of 64 cases of "undifferentiated" painful shoulders treated by Kuzell and his associates. 1222, 1227 Toxicity from the drug was frequent. [But many of their patients were treated with higher doses than are now considered desirable.—Ed.] Local injections of hydrocortisone into the area of the calcific deposit brought about relief of symptoms in 10 of 12 cases in one series, 1715 and in all of eight in another series. 1588

Intravenous mephenesin induced a temporary analgesia which was at times helpful in permitting adequate use of physical therapy. Needling, aspiration, and procaine infiltration, 1850, 1791, 1950 intravenous injections of an arsenic compound 100 and of adenylic acid, 1813 ultraviolet blood irradiation, 1468, 1834 oral tocopherols, 2022 and judiciously administered physical therapy 24, 463, 1791 were also again defended. Massive doses of vitamin B₁₈ were recommended. 1185 [The use of some of these remedies borders on necromancy, and is supported by as little evidence. Conspicuous in many papers is failure to appreciate the fact that in many patients acute shoulder pain is a self-limited condition.—Ed.]

Of 50 acute cases treated by stellate ganglion block, "excellent" results were obtained in 44 and "good" results in five more; while of 14 chronic cases, nine showed "excellent" results, three showed less improvement, and two no benefit. 802, 803 [As this group of patients with chronic pain were also given physical therapy and one was manipulated under anesthesia, the exact evaluation of the block is difficult. Evaluation of this paper is also difficult due to the author's loose use of the term "bursitis."—Ed.] Injection of the suprascapular nerves was also recommended. 802, 1320 Surgical removal of the calcific deposit was usually recommended for persistent pain. 446, 1077 Excision of the acromion process to prevent compression of the damaged sector of the cuff between the humerus and the acromion (originally recommended in 1943 by Watson Jones) was both recommended 1077 and opposed. 1424

"Frozen Shoulder." Two other local causes of pain in the shoulder were discussed: bicipital tendinitis, and the frozen shoulder (or adhesive capsulitis). In several comprehensive papers, DePalma traced the history, symptomatology, pathology and treatment of "frozen shoulder," stoutly defending the position that this condition is a sequel of bicipital tendinitis. 505, 506, 507, 508, 509 But arthrography of the shoulder using intra-articular diodone raised some doubt in this regard, showing almost complete obliteration of the inferior joint recess, but no abnormality of the bicipital tendon. Alternative concepts of the pathogenesis of the frozen shoulder were reviewed. 88, 2275

The clinical onset was usually insidious, and the progress of the disease extremely varied. Pain was less marked than in calcific tendinitis, but stiffness was greater. If the condition progressed in persons over 30 years of age, the arm sometimes became locked at the side due to firm adhesions of the entire capsule. Although ACTH and cortisone were of considerable benefit in some cases, 598 treatment in the early cases was discouraging and consisted mainly of properly administered physical therapy. The only cases relieved by manipulation were those in which the biceps tendon was ruptured. 507, 1423, 1050 Corticotropin was found helpful in controlling pain after manipulation. But some orthopedic surgeons felt that the only adequate therapy in the chronic case is the obliteration of the tendon sheath gliding mechanism of the long head of the biceps; this can be accomplished by transplantation of the tendon to the coracoid process or to the shaft of the humerus. 505, 1800

McLaughlin believed that many conditions may give rise to "frozen shoulder," but categorically stated that "no shoulder which moves through its normal range as often as a few times each day will ever become frozen." 1423

Other Causes of Shoulder Pain. Three cases of unusual lesions of the sternum associated with shoulder pain were reported. Repeated injections of streptomycin into the deltoid muscle was held responsible for "subdeltoid bursitis" in three patients. Russek felt that a "scapulo-costal syndrome" caused by "long-standing alteration of the relationship between the scapula and posterior thoracic wall" was a

"contributing factor in at least half of all cases of painful shoulders." Injections of procaine into trigger points in the scapular area combined with postural exercises were said to be an effective treatment. 1820

REFLEX SYMPATHETIC DYSTROPHY AND THE SHOULDER-HAND SYNDROME

These entities were reviewed in some detail in the Ninth and Tenth Rheumatism Reviews. Little of significance was added during the period covered by the current review except for reports of the effect of hormonal agents. Surprisingly few papers appeared on the subject, but those that did reported generally good results from the use of cortisone or ACTH.^{1918, 2020, 2071} With the use of cortisone, moderate to complete relief was obtained in 16 of 17 patients with the shoulder-hand syndrome following acute myocardial infarction.¹⁸²¹ However, sympathetic block still remained the most popular method of treatment, ^{356, 1855, 1859, 2083, 2136} although some did not recommend it.²³⁰⁴ After comparing the two methods of treatment, Steinbrocker, Neustadt and Lapin concluded: "Although a more satisfactory and more widely effective non-surgical treatment of the shoulder-hand syndrome is desirable, our results so far indicate that sympathetic ganglion block is the treatment of choice, with cortisone and/or corticotropin as a second choice." ²⁰³⁴ In Sudeck's atrophy following trauma, favorable ⁵⁶⁸ and unfavorable ¹⁷⁰⁵ results were obtained with cortisone.

Two Australian authors objected to the term "reflex sympathetic dystrophy," on the grounds that a reflex disturbance of the sympathetic system would not explain the changes encountered in the shoulder-hand syndrome. They suggested that the stiff shoulder could be explained by thickening and shortening of the inferior portion of the capsule, leading to obliteration of the inferior portion of the joint and thereby denying the humeral head the space required in its excursion during abduction.²³⁰⁴ Mogensen found a vasomotor disturbance in only three of six patients with the shoulder-hand syndrome, and questioned the usual concept of vasosympathetic imbalance in this condition. Since the reflex vasodilatation test he used was positive in 15 of 39 patients with periarthritis and in both of two patients with brachialgia, it was thought that pain in the arm may be the important factor in the vasomotor abnormalities.¹⁴⁸⁴

BRACHIAL NEURALGIA

Radicular Pain in the Upper Extremity

This subject, first treated under a separate heading in the Tenth Rheumatism Review, was discussed by numerous authors during the period of the current review. Unfortunately, the confusion previously pointed out still exists, and this subject, like that of the painful shoulder, suffers from lack of a uniform terminology. General summaries were written under the following headings: "painful conditions of the upper extremity," 1348 "painful states of the shoulder and arm," 117 "neurogenic brachialgia," 249 "neck and shoulder pain syndrome," 1019 "the neck, shoulder and arm syndrome," 411 "discognetic head, neck, shoulder, arm and chest pain," 1440 "cervico-brachial pain," 872, 1550, 1688 "brachial neuritis," 1580 "brachialgia" 250, 1650 and "the cervical myoradicular syndrome." 21 [There are, of course, inherent difficulties in grouping together various distinct pathologic entities on the basis of their most frequent symptoms. Nevertheless, in view of the frequency with which these conditions are encountered in the office of the practic-

ing physician and the difficulties experienced in their proper management, the present handling of the subject seems justified and desirable.—Ed.]

Pain was a variable symptom. Present in most cases, it may be entirely absent. It may be sharp and lancinating, or only a dull ache. It may be continuous through the waking hours, and then interfere with sleep, or it may be intermittent and noted only on certain movements or positions of head or arm. It may be localized in the region of the neck, or involve any part or all of an entire upper extremity. It may be noted in the thorax or upper abdomen, simulating visceral disease, or over the occiput. It is usually unilateral, but may be bilateral. Paresthesias, usually described as numbness and tingling, were noted by practically all patients, while vasomotor disturbances, with coldness of a hand, a dusky color or excessive sweating, were quite common. In cases of cervical disc pressure, three successive stages were recognized—an irritative phase, a compression phase and a paralytic phase. 12, 1440, 1880, 1881, 1672, 2220

Although not all authors were in agreement, most considered that the majority of conditions giving rise to these symptoms will fall into one of two great categories: abnormalities of the cervical vertebrae and their intervertebral fibrocartilages, or conditions causing pressure on the brachial plexus and subclavian vessels. A complete differential diagnosis, however, must include, in addition to the conditions discussed more fully below, the following: Pancoast's tumor, spinal cord tumor, extradural tumor, metastatic lesions of the vertebrae, syringomyelia, osteomyelitis, ununited fracture of the clavicle, herpes zoster, hypertrophic cervical pachymeningitis, basalar impression or platybasia, and cervical lymphadenitis. 1019, 1348, 1550, 1672, 2209 More than one pathologic condition was found in 29 of 104 patients with brachialgia. 10

Osteoarthritis of the Cervical Spine and Disc Lesions. Although acute traumatic rupture of the fibrocartilaginous annulus with herniation of the nucleus pulposus is rare in the cervical region, degeneration of the disc with anterior and posterior bulging is quite common. 1019 Recent studies of the normal and pathologic anatomy of the region have aided in understanding such lesions. It was pointed out that the posterior longitudinal ligament exerts a restraining effect limiting posteromedial displacement and predisposing to posterolateral prolapse of the disc. 1530, 1531 Particularly significant was recognition of the fact that the anterior wall of the cervical intervertebral foramina differs from foramina at lower levels by reason of a bony lip which projects from the superior surface of the vertebral body between the level of the nucleus and the corresponding nerve trunk and forms an anatomic barrier between disc and nerve root. This lateral lip is the most common site of degenerative change and osteophyte formation. 249, 250

The pathologic changes of disc narrowing and osteophyte formation with encroachment on the foramina were usually well demonstrated by x-rays taken in anteroposterior, lateral and oblique projections. ^{249, 1322, 1440, 1301, 1530, 1638, 1672} Differentiation between pressure from osteophytes and a disc lesion may or may not be possible clinically, but could usually be made by myelographic studies. ^{1322, 1530, 1672, 2018} Of 104 ambulatory patients with brachialgia, 70 were grouped under the diagnoses of cervical intervertebral disc protrusion and cervical osteoarthritis. There was a striking parallel in the findings in the two conditions, and it was suggested that they both are part of the same pathologic process. ¹⁰ Both condi-

tions should be treated conservatively in the early stages, using physical therapy, traction and a neck collar.^{21, 1256, 1530, 1531, 1550, 1672, 2018, 2058} One author recommended x-ray therapy as highly effective.¹³⁴⁰ Surgery may be necessary in obstinate cases. A "new" operation, based upon the use of a distraction bone

graft, was suggested.2018

Brachial Plexus Compression. The other great group, which includes various conditions causing pressure on the brachial plexus and subclavian vessels, remained somewhat less clearly defined. In this connection, the following terms have been used: scalenus anticus, cervical rib, costoclavicular, hyperabduction, 1820 scalenus minimus, 1251 coracopectoral, costopectoral, 1850 costobrachial, 1839 scapulocostal 2058 and "compression" 2200 syndromes. "Thoracic inlet neurovascular interference" 1088 was used as a general designation of the syndrome which could be produced by several mechanisms. The most frequently encountered term was the "scalenus anticus syndrome," but doubt as to the existence of such an entity was expressed. 1872 Vascular symptoms were more common in this group than in the cervical spine lesions. Adson divided the clinical manifestations into three groups: (a) minor constrictions interfering with certain uses of the arm; (b) occlusive changes in the subclavian artery with cyanosis and gangrene, and (c) disturbances of the sympathetic nervous system with vasomotor changes similar to those of Raynaud's disease. 12

It was emphasized that no one mechanism could explain all cases of this syndrome. Of 46 operations, in only seven cases was the syndrome due to pressure from the clavicle; in the remainder, compression was due to cervical rib or analogous fibrous band, or to the scalenus medius tendon. The scalenus anticus may be involved secondary to cervical spine lesions. The scalenus anticus and to primary scalenus anticus syndrome due to trichinosis of the muscle was reported. Some felt that the diagnosis of scalenus anticus syndrome was being made less frequently as knowledge of cervical spine pathology was improving. The results of surgery were found to be less satisfactory in patients with roentgen evidence of degenerative arthritis of the cervical spine.

Various maneuvers were recommended for determination of the mechanism producing this syndrome. The most common was the "Adson maneuver." In this, the patient sits with his hand resting on his knees, the examiner palpating the radial arteries. The patient then takes a deep breath, elevates his chin, and turns his head to the affected side. A prominent diminution of the radial pulse constitutes a positive test, and is presumably indicative of a cervical rib or scalenus anticus syndrome.12 The "hyperabduction maneuver" consists of elevating the affected arm in the lateral plane of the body and palpating the radial pulse with the arm extended high above the head. Obliteration of the pulse was thought to indicate compression of the artery in the space between the first rib and clavicle, 1550, 2209 but the test may be positive in normal persons.872 The "military position maneuver" consists of having the patient assume a stiff upright position and thrust the shoulders backward and then down. This, too, may obliterate the pulse due to compression between the first rib and the clavicle. 1848, 1550, 2209 The "downward traction maneuver" consists of palpating the radial pulse while pulling the arm downward. Diminution of the pulse is associated with postural defects, such as drooping shoulders, as well as compression at the costoclavicular area,1550 or scalenus anticus syndrome.411 Plethysmographic studies during the maneuvers may be of additional value. A carotid sinus syndrome may cause confusion.893

Treatment was dependent on the severity of symptoms. Conservative measures included avoidance of work or positions likely to bring about compression, the use of a sling when necessary, exercises to maintain the shoulders erect, and novocain injection of the scalenus anticus muscle. Operations included section of the scalene muscles, removal of supernumerary ribs, removal of a portion or all of the first rib or clavicle, and sympathectomy. 12, 411, 864, 872, 983, 1088, 1251, 1320, 1781

NONARTICULAR RHEUMATISM

The term "nonarticular rheumatism" embraces a large group of miscellaneous conditions with the common denominator of pain in, and stiffness of, connective tissue near but outside the joints. 608, 700 These disorders are considered as a group for convenience in classification, not because of any common etiologic or clinical characteristics. 508 Such nonarticular forms of rheumatism are more prevalent than rheumatoid arthritis, rheumatic fever or gout. 348 While some forms of nonarticular rheumatism, such as bursitis and tendinitis, present well-defined features, others—particularly those referred to as "fibrositis" and "my-algia"—are poorly defined, without clear-cut etiology or pathology, and they hold different connotations to different physicians and in various parts of the world. [In this review the term "fibrositis" is not used as a synonym for nonarticular rheumatism, but refers to the symptom complex discussed in a subsequent section as one of the subtypes of nonarticular rheumatism. The sections dealing with "The Painful Shoulder," "Brachial Neuralgia" and "Backache and Sciatic Pain" also refer to certain conditions which can be considered as forms of nonarticular rheumatism.—Ed.]

Diseases of Bursae (Bursitis). Acute or chronic inflammation may involve any bursa in the body. Of the superficial bursae which lie between bony prominences and skin, the olecranon and prepatellar were the most common sites of bursitis. Among the deep bursae which lie between muscles or tendons and moving bony prominences, bursitis occurred most frequently in the subacromial, subgluteal, iliopsoas, supra-trochanteric, semimembranosus, pretibial and Achilles' bursae. 58, 54, 408, 408, 700 The etiology was usually obscure. Superficial bursae sometimes became inflamed after repeated or chronic trauma and irritation of their walls. Unusual activity, exposure to dampness and cold, and infection were other etiologic factors suggested. 698 Specific infections such as tuberculosis should be considered in the differential diagnosis of chronic bursitis. 1141, 1985 Case reports illustrating possible confusion of several unrelated conditions with bursitis were presented and the differential diagnosis was discussed. 307, 1593 The clinical features, diagnosis and treatment of bursitis in the various anatomic sites outlined above were described in detail.^{54,698} Subacromial bursitis, the most common type, is discussed in the section on "The Painful Shoulder."

Tuberculous bursitis affected the subacromial bursa in six patients, 1141 the bursae about the greater trochanter of the femur in eight patients, and the olecranon and ischial bursa in one instance each. 1985

Treatment. Analgesic drugs, rest and immobilization with slings or splints, heat and assisted and active exercises as pain subsided, were the basic measures recommended. Cold applications were used if heat caused aggravation of pain. ^{698, 981} Aspiration was performed if the bursa was acutely inflamed or distended. Local injections of cortisone were reported effective, ¹⁵⁸⁷ but subse-

quently were supplanted by hydrocortisone injections directly into the bursa as an important addition to the treatment of this disorder. Stray therapy 1602 and local injection of the bursa with procaine or procaine-amide-hydrochloride 1336 were favored by some. Many other measures were advocated which require further assessment or have not been generally adopted to date. These included ultrasonic therapy, 1988 vitamin E, 1155, 2022 pregnenolone acetate, 1723 intramuscular adenosine-5-monophosphate, 1813 intravenous iron cacodylate, 160 counterirritating liniments 1366 and mephenesin. Surgical removal of the calcified deposit was advocated if conservative treatment failed to provide relief.

In tuberculous bursitis, administration of streptomycin and PAS and surgical excision of the bursa and all its ramifications and sinuses were the treatment of choice. If surgery was contraindicated, repeated aspiration and prolonged im-

mobilization in plaster were advocated. 1141, 1985

Tenosynovitis and Tendinitis. Inflammation or degeneration of tendons and tendon sheaths may occur in association with frank arthritis, or may be independent of joint lesions.³⁴⁸ Unusual manifestations of rheumatoid tenosynovitis were described.¹¹⁵⁶ Tuberculous tenosynovitis pursues a chronic, slowly destructive course and may involve any tendon sheath, the wrist being the most common site. In one series of 52 patients, the sexes were about equally affected; the right side of the body was involved twice as often as the left. Open operative excision produced better results than rest, immobilization and supportive care, the conventional treatment of tuberculosis.¹⁸² [Most of these patients were treated before the advent of streptomycin and other tuberculostatic agents.—Ed.]

Etiologic factors in nonspecific tenosynovitis included single or repeated local strain or trauma and repetitive stereotyped movements requiring effort and speed. Tendons which move around corners or under ligaments were thought to be particularly susceptible. The extensor and flexor tendons and their sheaths in the dorsal and volar carpal tunnels at the wrist were most often involved, with the anterior and posterior tibial and peroneal tendons at the ankle next in frequency. Local pain, swelling and tenderness, with weakness of the affected muscles, were the usual manifestations. Some subsided spontaneously, others ran a prolonged course, with exacerbations on resuming activity. Treatment included immobilization, heat, analgesics and graded exercises.^{848, 2117} Local injection of hydrocortisone,⁷⁰⁰ x-ray therapy and surgical excision of the sheath ⁷⁵⁰ were recommended for those failing to respond to conservative therapy.

Stenosing Tendovaginitis. The hand was the most common site. Quervain's disease (stenosing tendovaginitis of the abductor pollicis longus and extensor pollicis brevis as they pass through their common sheath over the radial styloid) was frequently associated with anomalous arrangement of these tendons and their sheaths; but such anomalies were not considered to be etiologically significant. An important physical sign was the production of pain by ulnar deviation of the hand with the thumb held across the palm by the flexed fingers. Snapping, locking and crepitus were not features of this disease. Conservative treatment was usually unsatisfactory, and surgery with early resumption of active movement was the treatment of choice. 848, 1287, 1801, 1818, 1781, 2017, 2181

Stenosing tendovaginitis may also involve the tendons of the flexor pollicis longus (frequently in infants), flexor digitorum sublimus and profundus, extensor carpi radialis longus and brevis, extensor pollicis longus, extensor indicis proprius, extensor di-

giti quinti proprius, extensor carpi ulnaris and flexor carpi radialis. Stenosing tendovaginitis of the flexors of the fingers and thumb produced pain, snapping and locking in flexion, the so-called "trigger finger" or "trigger thumb." Treatment was similar to that in Quervain's disease. Reviews of large series of patients, covering the anatomic, pathologic and clinical features, as well as diagnosis and treatment, were the subjects of several reports. 305, 848, 1237, 1238, 1301, 1318, 1731, 2017, 2184 Stenosing tenosynovitis of the foot and ankle most commonly affected the peroneal tendons; occasionally the dorsal and medial tendons were involved after trauma. 308 Anomalies were found at operation in four of 11 cases of synovitis of the posterior tibial tendon sheath. 750

Noncalcific Tendinitis. Tendinitis may occur in tendons without synovial coverings. The rotator cuff and biceps tendons at the shoulder were most commonly involved. Other sites were the common tendinous origin of the forearm extensors from the lateral humeral epicondyle ("tennis elbow"), the wrist extensors proximal to the sheath beneath the dorsal carpal ligament, the anterior and posterior tibial tendons proximal to the ankle, the triceps brachii and Achilles' tendons. It was stated that any place of insertion of tendons into periosteum could be the site of recurrent tendoperiostitis. Tendinitis at the insertion of the common extensor tendon to the head of the first phalanx of the fingers was attributed to recurrent occupational strain in three patients, 306 and three instances of focal degeneration of the patellar tendon were reported. The term "peri-tendinitis crepitans" was advocated to describe inflammatory changes confined to musculotendinous junctions. 2117 In addition to immobilization, heat, analgesics and graded exercises, various other forms of therapy were recommended, including local procaine injection, 608, 700, 2027 x-ray therapy, 1602 phenylbutazone, 1222 adenosine-5-monophosphate, 1813 vitamin E 1155, 2022 and ultrasonic therapy.

Calcareous Tendinitis. Calcification may occur in tendons at their bony attachments, in the substance of the tendon itself, at times extending into the adjacent muscles (myotendinitis calcarea) or the peritendinous connective tissue (peritendinitis calcarea).1834 The basic lesion was considered to be a focal degeneration or necrosis of tendinous tissue with deposition of calcium in the necrotic collagenous tissue; formation of a "calcium granuloma" and secondary inflammatory reactions commonly occurred. This sequence of events was well documented in study of material removed from the shoulder in 55 patients. 1826 Comparable lesions were described in tendons about the wrists, elbows, fingers, hip. knee and ankle. 20, 441, 702, 1007, 1281, 1474, 1580, 1647 Wrist involvement was most often on the ulnar side, with calcification in the tendon of the flexor carpi ulnaris or in the bursa beneath this tendon near its insertion into the pisiform bone. 792, Some considered the condition self-limited and advised only immobilization and heat. 792 Others advocated x-ray therapy. 441, 1474, 1602 "Washing out" or surgical removal of the calcified material was advocated if conservative measures were unsatisfactory. [The frequency of spontaneous remission makes the therapy difficult to evaluate.-Ed.] Sandström suggested that one type of intervertebral disc calcification may be produced by the same mechanism and, like calcareous tendinitis elsewhere, be capable of producing pain, tenderness, spasm and limitation of motion.1834

Dupuytren's Contracture. The etiology of this abnormality of the palmar fascia remained obscure. Familial predisposition was again emphasized. 1495, 1809 Local trauma, occupation and endocrine factors were not considered etiologically significant, 947, 1495, 2022 although some felt that repeated minor traumas in predisposed individuals were causative factors. The lesion was considered

to be a low-grade inflammation associated with excessive scar tissue formation, with progression from an active stage of fibroblastic proliferation to later, acellular stage in which collagen fibers predominated. However, Warren was not impressed by evidence that the reaction is primarily one of inflammation; in his opinion, the lesion appeared to be the result of the growth and infiltration of palmar fascia into surrounding structures, becoming adherent to skin, tendons and joint capsule. "The conception of this lesion as a benign neoplasm of the palmar fascia best explains the clinical and pathologic process." ²¹⁹⁶

Well recognized clinical features were again summarized. 1893, 1809 The association of dorsal knuckle pads was noted in eight of 36 patients in one series; histologic section of such a dorsal nodule disclosed an appearance similar to the early active cellular phase of the palmar contracture. 1809 Dupuytren's contracture was associated with Peyronie's disease in 10 patients; histologic similarities in the two conditions led to speculation that they may have a common patho-

genesis.2181

Opinion regarding the value of vitamin E administration remained divided between proponents 1809, 2022 and skeptics. 1383, 1747 A carefully planned objective study gave evidence of limited but definite benefit from this vitamin. Casts were made of 26 affected hands in 19 patients, and measurements made of the volume of the palmar concavity and the angle of contracture of the fifth finger. After 300 days of administration of d-1-alpha-tocopherol acetate in doses of 300 mg. per day, there was definite improvement with respect to palmar concavity in 23 instances and to angle of finger contracture in 15 instances. The magnitude of the changes was only moderate; the benefit was substantially maintained 200 days after the drug was stopped, but regression occurred by 335 days after its discontinuation. [It should be noted that the subjects in this study had longstanding chronic contractures; the average age of the subjects was 74 years.—Ed.]

The details of technic of surgical treatment were described by several authors. 72, 884, 1883, 1495, 1809, 1888 Reported results were consistently good. Postoperative administration of cortisone tended to lessen edema and scar formation and permit more effective mobilization. 125 X-ray therapy was said to be beneficial during the early stages of fibroblastic proliferation, but its effects were not consistent or sustained. 1495 Two patients treated with microwave diathermy were reported to have obtained relief

of finger flexion deformities.2256

Calcinosis. Additional cases of circumscript 883, 1667 and universal 513 calcinosis were reported. Recognized features of each condition 1667 and their frequent occurrence in patients with scleroderma 899, 883 and dermatomyositis 2236 were again noted.

Soft Tissue Calcifications and Ossifications Associated with Spinal Cord Lesions. Of a group of 30 paraplegic patients, 16 showed single or multiple calcifications, commonly undergoing transformation to true bone. These always occurred below the level of the cord lesion. It was considered that they were related to the interruption of nerve pathways, particularly of the sympathetics, with reversion to embryonic tissue and bony metaplasia. 1287

Myositis and Myalgia

Myositis Ossificans Progressiva. This rare, progressive disorder of mesodermal differentiation is characterized by gradual calcification or ossification in connective tissue about muscles, tendons, aponeuroses, fascia and ligaments, ler 'ing eventually to bony ankylosis and almost complete immobility of the entire body. Since the calcification occurs in the connective tissue about the muscles rather than in the muscles themselves, fibrositis ossificans progressiva was considered a more appropriate name. Five additional case reports were recorded.⁴⁷⁵⁴, ²²¹⁴ Cortisone therapy was associated with marked relief in one patient in the early stages of the disease, but was of no benefit to another patient in a more advanced stage.¹⁷⁵⁴

Myositis Fibrosa Generalisata. Generalized myositis fibrosa, one of the rarest muscular disorders, develops insidiously, with gradually increasing stiffness in the limbs, interfering with normal voluntary movement, without pain or fever, progressing till the patient becomes bedridden and debilitated regardless of treatment. Eleven cases from the literature were reviewed and one further case history was reported; it was suggested that this disorder is closely related to, if not an actual variant of, progressive muscular dystrophy.²⁰⁸⁸

Relapsing Myositis. This term was applied by McLetchie and Aikens to a clinical entity not previously described in the literature. The patient, a 33 year old man, was observed over a 17 month period during a relapsing, febrile illness characterized by numerous tender muscular swellings, protean in distribution, sometimes large in size, almost all of which completely regressed, with ultimate restoration of normal function. Muscle biopsies disclosed widespread patchy necrosis of muscle fibers; the lesions were distinguished from dermatomyositis by the absence of vascular lesions and of fibrinoid degeneration of collagen and by the normal appearance of the mesenchymatous investment of the muscle. A permanent heart block developed during the course of the illness. 1426

Epidemic Myositis or Myalgia (Epidemic Pleurodynia: Bornholm Disease). A considerable number of epidemics in various parts of the world were reported, stressing the clinical features, and epidemiologic and virologic studies. ⁴⁸³, ⁵²⁶, ¹⁰²⁴, ¹²⁵³, ¹⁴³¹, ¹⁵⁵², ¹⁶¹⁰, ¹⁷⁸⁹, ²⁰⁸², ²¹²⁰, ²¹⁰³ Complications included orchitis, pleurisy and meningitis. Orchitis was not uncommon in adults during the second week of the illness, leaving no residual testicular atrophy. ¹⁵⁰² Recurrences were frequent in some epidemics. ¹⁶⁵², ²¹⁰³

Extensive studies were carried out on Coxsackie viruses and their etiologic role in epidemic myalgia. 77, 279, 522, 526, 1032, 1024, 1258, 1448, 1616, 1759, 2082, 2128, 2128 There was impressive evidence from isolation of virus and development of neutralizing antibodies that one or more strains of Coxsackie virus, Group B (Dalldorf), are pathogenic for man and result in the clinical disease recognized by this name. While recent American epidemics have been attributed to a Coxsackie virus of Group B, Type 3 (Dalldorf), it was considered possible that different epidemics might be caused by other strains within this group.

Myalgia and Myalgic Spots. Myalgia and myalgic spots were attributed to a variety of apparently unrelated etiologic factors, including infections, allergies, climatic conditions, trauma and psychic stress. It was thought that through the common factor of vasomotor imbalance, all of these could produce local areas of decreased blood flow, with resulting hypoxia or anoxia in muscles and tendons. ^{794, 795, 797} Others contended that the diffuse muscle aching and local tender spots constituted pain referred via reflex pathways from visceral or somatic tissues, and were accompanied by tenderness due to liberation of a "pain substance," ¹¹³⁴ or to disturbance of sympathetic control of a "glomus bodyorgan." ²¹⁴¹ Other causative factors incriminated included food allergies ^{1112, 1716} and faulty posture during sleep. ⁴⁴ Various forms of treatment were recommended: ultrasonic therapy, ¹⁸⁸⁸ exclusion of allergenic foods from the diet, ^{1112, 1716} and injection of the tender "trigger areas" with local anesthetic solutions. ^{794, 795, 797, 2027}

Electromyographic studies in 63 persons with occupational myalgia indicated a certain degree of hyperirritability of the affected muscles and evidence that those afflicted used more muscle power in typing than did control subjects. ¹⁸⁴¹ Gordon also believed that overuse of muscle can cause isolated myalgia. Eight patients with sharply localized pain and tenderness at the lower angle of the scapula, over the insertion of the serratus magnus, were all doing repetitive work involving this muscle; symptoms were relieved by change of activity. ⁸⁰¹

Fibrositis

Much confusion and controversy surrounded this subject. This was due in part to lack of uniform diagnostic criteria, in part to the use of multiple alternative terms such as myalgia, myofibrositis, myofasciitis and muscular rheumatism, and in part to the tendency of some to apply the term "fibrositis" to all types of nonarticular rheumatism. Nevertheless, it was felt that even after separation of such definable entities as tendinitis, bursitis, fat herniations, psychogenic rheumatism, etc., there remained a group of individuals with diffuse or localized soft tissue pain and stiffness with certain qualitative characteristics, in the absence of clinical, laboratory or x-ray abnormalities, in whom the diagnosis of "fibrositis" appeared justifiable.343, 698, 1544 Since this diagnosis was based on a clinical symptom-complex rather than on any pathologic tissue changes, the term "fibrositis-syndrome" was recommended. 813 [It is evident that much confusion stems from the fact that a symptom complex was labeled with a word with specific pathologic implications.-Ed.] With the recognition that various pathologic lesions of joints, ligaments, intervertebral discs and bursae are responsible for what was hitherto considered to be fibrositic pain, the use of fibrositis as an exact diagnosis has been subjected to criticism. 50 "It may well be as convenient a term as 'rheumatism,' but it seems likely that it will gradually lose its usefulness as more exact diagnosis becomes possible" (Tegner 2111).

Etiology. The earlier concept of local inflammatory changes in muscle and connective tissue was generally discredited; such lesions have not been found in biopsy specimens. 698, 818, 981, 1544 Many considered that this condition was not a clear-cut disease entity, but a syndrome brought about by a variety of different factors such as trauma, fatigue, psychic stress, physical strain, cold, dampness and possibly endocrine dysfunction. 698, 818 Hypoxia or anoxia in muscle and connective tissue was postulated as the common mechanism by which such diverse factors can produce local "myalgic spots" and diffuse aching. 794, 795, 797 Others contended that the diffuse achieves achieves the contended that the diffuse achieves the contended that the contended the co ing and myalgic spots constituted pain referred via reflex pathways from visceral, cutaneous or somatic tissues.^{1134, 1888} It was suggested that fibrositis resulted from localized periostitis or osteitis of the underlying bone.1243 [Histologic evidence supporting this speculation was described, but vaguely.-Ed.] A further theory proposed that "primary fibrositis" was due to disturbed muscle nutrition caused by dysfunction of the osseomuscular vascular channels which were demonstrated to exist between bone metaphyses and the overlying muscle.926 Focal infection was not considered etiologically significant in most cases, 700, 813 although some felt it might act as a "trigger mechanism" in certain instances.981 Many cases of so-called "fibrositis" were attributed to mechanical strain on supporting tissues due to obesity, faulty posture and inadequate musculature, 1200, 1891 and to faulty postural habits during sleep.44 Food allergies were incriminated by some. 1112, 1716 Psychologic factors were recognized more and more widely, and many considered that psychosomatic "tension-states" were the most important, if not the sole etiologic factor in many patients. 813, 981, 1087, 1821

Clinical Features. Pain, stiffness, soreness and fatigue were the usual symptoms. Paresthesias were noted by some. The pain was generally described as a dull ache, worse after rest, improving with moderate activity but recurring with the onset of fatigue, often precipitated or aggravated by cold, drafts, dampness and emotional upsets. Pain was relieved at least temporarily by heat, salicylates, alcohol and physical and mental relaxation. Physical examination usually revealed no abnormality, but some patients exhibited limited movement of the affected part, muscular tenderness (diffuse or in localized "myalgic spots"), and at times vague nodular thickenings in the areas of tenderness. No symptoms or signs of constitutional illness other than fatigue or lack of energy were evident. The onset was variable, sudden in some, insidious in others. The course could be acute, subacute or chronic, with exacerbations and remissions. The most frequent sites of involvement were the lower back, thigh, neck, shoulder and hand, and the interscapular, thoracic and gluteal areas. 898, 813, 981, 988, 1554 The syndrome of "fibrositic headache" was discussed in detail. 1883 The hemoglobin, leukocyte count, sedimentation rate, x-ray studies and biopsies from affected areas showed no consistent abnormality. 698, 818, 981

Diagnosis. "Fibrositis is a useful diagnosis. It requires the very briefest history; a single word may be sufficient—pain. For physical examination a single prod eliciting tenderness may be enough." ⁵⁰ [Thus was superficial diagnosis of this condition ridiculed.—Ed.] It was recommended that the diagnosis of fibrositis be confined to those patients exhibiting the typical clinical syndrome described above, with no evidence of underlying disease or disorder which could be responsible for secondary "fibrositic" symptoms. The differentiation from the early stages of joint, bone and muscle diseases, particularly rheumatoid arthritis, may be very difficult and in some instances may be possible only as the disease runs its course and other features appear. ⁶⁹⁸ Similarity to symptoms produced by diseased intervertebral discs was again pointed out. ¹⁸¹⁰

Treatment. Basic measures included reassurance concerning the absence of disabling disease, explanation of the nature of the symptoms, adequate rest, and the use of salicylates, local heat, massage, postural and general stretching and relaxation exercises. Correction of postural faults and weight reduction of the obese were advised as indicated. Foci of infection were treated on their own merits. Adjustment of occupation and environment was advisable in some instances. Physical and recreational activities which did not induce fatigue or aggravate symptoms were encouraged. 625, 698, 700, 813, 981, 1200, 1691 Adjuncts to physiotherapy, such as ultrasonic therapy, 1988 microwave diathermy, 2256 counterirritating and vasodilating liniments, 1366 local injection of anesthetic oils, 1316 and the use of mephenesin, 941,1087 were advocated [but not widely accepted as valuable procedures-Ed.]. Oral phenylbutazone produced "prompt relief in three of four patients with acute myofibrositis." 1222 Injection of novacain, procaine or procaine amide hydrochloride into local tender areas continued to have many advocates, 698, 794, 795, 797, 818, 981, 1200, 1691, 1883, 2186 Proper selection of patients and limitations in the usefulness of procaine injections were stressed. 806, 2027 Adequate psychologic appraisal and skillful psychotherapy were considered of basic importance in many cases. 813, 981, 1087, 1831

Injection of painful sites with cortisone "relieved 17 of 34 patients with myofascitis." 1587 The use of systemic cortisone was considered unwarranted. 698, 700 Pre-

vious claims for the effectiveness of inunctions of adrenaline cream were not confirmed in two controlled studies. $^{316,\ 1249}$ Other forms of treatment of unconfirmed value included intramuscular vitamin $B_{12},^{981}$ local injections of camphor and benzyl salicylate in oil, $^{1243}, ^{1877}$ elimination of allergenic foods from the diet, $^{1112}, ^{1716}$ intramuscular pregnenolone acetate, 1723 oral vitamin E, 2022 vitamin E ointment, 1155 histamine iontophoresis 1200 and antihistaminic drugs. 1087

Disorders of Fatty Tissues

Herniation of Subfascial Fat. Copeman's concept of painful distention of fat lobules due to edema and their herniation through deficient areas of fascia, with the production of "fibrositic" symptoms, was supported by observations in 302 patients with backache. 946 Such herniations were most commonly found in the lumbosacral or sacro-iliac regions as single or multiple tender, painful nodes. Pain was at times severe, and some patients experienced difficulty in moving at the onset of an episode. 946 Such pannicular hernias can be differentiated from diffuse panniculitis and relapsing febrile nodular panniculitis. 648 Relief was obtained by local injections of procaine, and this therapy could be repeated as needed. Individuals thus relieved temporarily by local injections may expect permanent relief from surgical removal of the nodules. 648, 698, 946, 981, 1567, 1864 If pain was not relieved by local injections with novocain, there was little likelihood that operative removal of the nodules would prove beneficial.946 Resection of subfascial fat tissue at the sites of "trigger areas" of the lumbodorsal fascia was said to result in relief of chronic backache. 528, 529 [These surgical claims would be more impressive if supported by some objective data or by controlled observations.-Ed.1

Other Lesions in Fat of Normal Distribution. A 30 year old obese woman developed pain and tenderness over the anterior aspect of the patella following direct trauma. This was considered to represent a traumatic prepatellar bursitis, but at operation a fat pad was found superficial to and adherent to the normal prepatellar bursa. Complete relief followed excision of the fat pad, which showed no abnormality on microscopic examination.⁸⁰⁷ [Similar painful tender areas in subcutaneous fat of normal distribution were described in the Tenth Rheumatism Review.—Ed.]

Panniculitis. Pain arising in abnormal fat deposits was said to occur most commonly at the menopause, usually accompanied by rapidly developing fat accumulations in the trunk and limbs. Biopsies revealed thickening and increased density of collagen bundles in the reticular layer of the dermis, with no evidence of inflammation, no cellular reaction, and no abnormality in the fatty tissue. The term "panniculitis" was therefore considered a misnomer. The condition tended to clear up spontaneously; treatment with reducing diet, salt restriction, general exercises, hydrotherapy and

massage was recommended.⁹⁵

Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease). Additional cases were recorded and the established clinical and pathologic features were reviewed.^{601, 706, 882, 887, 1815, 1760, 1918} Splenomegaly was reported in some.^{882, 887} Similarity to the manifestations of various "collagen diseases" was again noted.^{1815, 1760, 1918} In one patient phlebosclerosis was prominent.⁶⁰¹ The etiology remained obscure. Allergy, infection, trauma, disordered fat metabolism, endocrine disorders, dietary deficiencies, renal insufficiency and ingestion of halogens all have been implicated but were not consistent etiologic factors. Virus studies of biopsied tissue were negative.¹⁹¹³ A relationship to Hodgkin's disease was suggested in some cases.^{882, 1913} Treatment was mainly supportive and symptomatic. Sulfonamides,

the various antibiotics, heavy metals, x-ray therapy, quinine, viosterol, thyroid and pituitary extracts, androgens, antihistaminics, para-aminobenzoate and numerous other therapeutic agents advocated in the past have not been consistently beneficial. Regression of lesions during treatment with cortisone 898, 1913 and with corticotropin 245, 1315 was noted, but some patients failed to respond during a subsequent relapse. 898, 1913

Psychogenic Rheumatism

Psychogenic rheumatism was defined as "the rheumatic manifestations of a psychoneurosis." It was characterized by arthralgia, muscle and tendon pain, stiffness and interference with joint motion resembling those seen in common forms of arthritis and "fibrositis," occurring in persons in emotional conflict. Absence of joint changes on clinical and roentgenologic examination, normal laboratory observations and good organic health were characteristic. Bizarre postures not conforming to anatomic changes and recognition of other evidences of psychoneuroses were helpful diagnostic features. Some felt that psychogenic rheumatism should be differentiated from "fibrositis" on the basis of failure to respond to measures usually effective in the relief of "fibrositis," and because of the inconsistency and atypical localization of symptoms in the patient with psychogenic rheumatism. Solly on a psychogenic data the typical "fibrositic syndrome" could arise solely on a psychogenic basis. This disorder was reported to be one of the more common forms of nonarticular rheumatism seen in civilian and military practice.

It was emphasized that people could become physically sore and stiff from mental as well as physical causes. While some presented manifestations of frank and at times severe psychoneuroses, others did not merit such a definite diagnosis but were emotionally unstable, reacting in an exaggerated way to what most people would consider ordinary trials of life by becoming tense, keyed-up, "tied in knots" and unable to relax. It was proposed that such psychic stress acted through some peripheral mechanism, possibly a local neuromuscular or vascular dysfunction, to produce muscle tension which would rise and fall with fluctuations in emotional tension. This could in some way stimulate muscle pain mechanisms to produce aching and tenderness and, by nervous reflex pathways, result in "trigger points" and referred sensations.813 Further reference was made to the importance of sustained, excessive muscle tension associated with chronic emotional disturbances in the production of soft-tissue pain, and reports of increased electromyographic potential in skeletal muscles of tense, anxious individuals with such pain were quoted. These patients were described as "rigid, insecure, resentful and hyperkinetic, exhibiting a characteristic pattern of dealing with stressful life situations by vigorously and relentlessly attacking their problems." Their continual struggle between dependent needs and resentment and their aggressive drives was reflected in excessive muscle tension sufficient to require voluntary neuromuscular effort to overcome it, eventually resulting in impaired muscular efficiency and susceptibility of muscle and other supporting structures to minor trauma, with subsequent pain. 1321

Reassurance concerning the absence of any disabling or serious disease and patient explanation of the nature of the disorder were said to form the basis of treatment. Prolonged psychotherapy was necessary in some instances to effect a rationalization of life problems and adjustment to emotional conflicts.

Efforts should be directed toward educating the patient to relax both physically and mentally, with the aid of mild sedation if necessary. 698, 981

Tumors of Synovial Tissues

Hemangioma. Cavernous hemangioma of the knee, although uncommon, was stated to give a characteristic clinical picture. It occurred more frequently in females, and may be preceded by trauma. It may present with pain, limp, limited movement and a tender, spongy swelling which may be diminished by elevating the limb. Excision of the pedunculated type was advised, but for the diffuse type, roentgen therapy or injection of sclerosing solutions was preferred.¹⁰²⁸

Osteochondromatosis and Synovial Chondromatosis. In this condition, bony or cartilaginous nodules develop singly or in clusters in synovial membrane. These nodules become extruded toward the joint surface, at first retaining hairlike pedicles which ultimately break, leaving the body loose within the joint cavity. Single joint involvement was the rule, affecting the knee, elbow, ankle, hip, shoulder, hands and feet, in decreasing order of frequency. Although disabling secondary osteoarthritis was a common sequel, this condition could be differentiated from chronic arthritis in the great majority of cases by accurate clinical and radiologic examination. An unusual instance of acute, disabling osteochondromatosis of the hip was reported, The peroneal tendon sheath was the site of osteochondroma formation in one case.

Pigmented Villonodular Synovitis. This term was considered synonymous with xanthomatous, myeloid, giant cell or polymorphous cell synovial tumor, benign giant cell synovioma, xanthogranuloma, and hemorrhagic villous synovitis. 1478, 1879 Some looked upon it as a quasitumorous or local proliferative reaction, 1061, 1879 or a villous synovitis which perpetuates itself because of hemorrhage. 661 Others felt that it is a true benign neoplasm. 2204 In five reported cases the condition presented as a chronic mono-articular lesion, often with palpable tumor, of the knee or ankle. Aspiration produced sterile serosanguineous fluid, sometimes laden with cholesterol crystals. Surgical excision of involved synovium followed by x-ray irradiation was the recommended treatment. 1478 An unusual instance of involvement of the ileopectineal bursa was reported. 2226

Giant Cell Tumor of Tendon Sheaths. The exact nature of these tumors continued to be the subject of disagreement. The microscopic features were similar to those of pigmented villonodular synovitis; some considered them to be a form of tenosynovitis, 1061 others felt that they were true benign neoplasms. 2294 In series of 85 patients 2294 and of 41 patients 666 the occurrence of this condition conformed to the recognized age peak in the middle decades, the more frequent occurrence in women, and the predilection for location in the hands and fingers. Bone involvement, usually limited to erosion, was not uncommon if it was looked for carefully. 666 Treatment consisted of excising the local lesion as completely as possible. Postoperative recurrences were not uncommon; they developed in 25 of 54 patients followed by Wright. 2294 Kestler described six cases in which rheumatoid tenosynovitis simulated tumor of the tendon sheaths. 1156

Synovial Sarcoma (Malignant Synovioma). This relatively uncommon, highly malignant tumor was regarded as presenting a varied histologic picture, depending on the potentialities of differentiation of connective tissue cells.⁶⁶¹, ⁸⁹¹, ¹¹⁰⁸ Though more commonly found in areas where synovial membrane is present, there was little or no evidence that they actually arose from a synovial surface.⁶⁶¹ "The classification is histologic, not histogenetic, in basis" (King ¹¹⁶⁸). Fiske felt that synovioma was an unfortunate term, and preferred the term "parasynovial sarcoma." ⁶⁶¹ [The confusion is reflected in occasional reports of "benign synovioma." ¹⁰¹²—Ed.]

Tillotson and co-workers tabulated 194 acceptable cases from the literature, and added 28 cases of their own. 2180 Other series added 47, 2295 17 877 and 21 cases. 1168 Individual case reports were also recorded. 171, 211, 281, 422, 450, 1819, 1483, 1471, 1900, 1990, 2069 The variable clinical manifestations included pain, limp, limited movement, and palpable tumor or swelling. Most gave no history of trauma. Though it occurred at any age, 80% of patients were between 15 and 50, with a slightly higher incidence in males. The knee, ankle and foot, thigh and hip, the elbow and the hand were the most common sites. A synovioma of the anterior abdominal wall, presumed to arise from the sheath of the internal oblique, or from an adventitious bursa, was reported.171 Growth was usually slow and insidious, spreading along tissue planes and metastasizing late, most often to regional lymph nodes and lungs but also at times to bone, liver, skin, bladder, bowel, heart, thyroid, brain, and paravertebral and retroperitoneal soft tissues. While an accurate diagnosis could not be made on the roentgenologic findings alone, certain radiographic features were relatively common.^{877, 1899} Treatment of choice was amputation after the diagnostic biopsy. Results of treatment were poor. Eighty per cent were dead within five years after operation.²¹⁸⁰ Symptoms due to metastases were relieved in some cases by roentgen therapy or by nitrogen mustard. 2069

CONGENITAL DEFECTS

Hereditary "crooked little fingers" were classified on the basis of mechanism of production rather than outward appearance as: (1) incomplete ossification, (2) short tendon, and (3) fused ossification. A common example of the first group is clinodactyly, characterized by radial deviation of the terminal phalanx of the fifth finger due to a localized area of arrested ossification on the radial side of the shaft of the middle phalanx. This trait was inherited as an autosomal dominant in both sexes, with a slight lack of penetrance. Its estimated incidence was one per 1,000 of population.

A case of osteochondrodystrophy (Morquio-Brailsford's disease) presented findings similar to osteochondritis dissecans of the knee. Because of certain clinical similarities and suggestive laboratory findings in one case of Ehlers-Danlos syndrome, it was suggested that this condition may be due to adrenocortical hyperfunction. The evidence for this hypothesis is far from impressive.—Ed.]

ARTICULAR DISEASE ASSOCIATED WITH PRIMARY BONE PATHOLOGY

Hypertrophic Osteoarthropathy. A detailed study of the skeletal lesions in seven cases of generalized hypertrophic osteoarthropathy (six associated with pulmonary disease, one with congenital heart disease) permitted Gall, Bennett and Bauer to develop a pattern of the pathogenesis of this condition. Productive periostitis involving the long bones of the extremities constituted the most striking finding. The inflammatory periostitis was characterized by lymphocytic and plasma cell infiltration, subperiosteal new bone formation, and the production of a pseudocortex which ultimately fused to expand the original cortical bone. The findings were suggestive of intermittent activity of the periosteal lesion. Joints in the involved extremities were the seat of chronic synovitis, mild to moderately severe, and nonspecific in character; this was associated with degenerative changes in the articular cartilages. Clubbing of the digits appeared to result from an increase in soft tissue bulk. 723

Attention was again called to the fact that the joint symptoms may precede those of pulmonary disease, and that the condition may closely simulate rheumatoid arthritis. 680, 684, 1818 Of 14 cases of hypertrophic osteopathy associated with pulmonary

neoplasm, in 13 the neoplasm was located in the periphery of the lung.¹⁷²⁶ The mechanism of production of the osteopathy and associated clubbing of the fingers remained obscure.⁷²⁸ Increased blood flow in clubbed fingers was demonstrated by measurement of heat elimination, and apparently was not due to action of vasodilator nerves. A reduction in blood flow led to regression of clubbing, as did successful treatment of an underlying intrathoracic condition.²²⁶⁷

Although hypertrophic osteoarthropathy was usually associated with chronic pulmonary disease or congenital heart disease, it may accompany many visceral lesions. 1725, 2257 It may occur as a hereditary anomaly entirely unaccompanied by evidence of organic disease, behaving in the manner of a single mendelian dominant without sex heritage or influence. 2103 A case of osteoarthropathy associated with exophthalmic goiter was presented by Greene, who also discussed four other cases of "thyroid acropathy," pointing out that all five were in males, and all were associated with severe exophthalmos and hypothyroidism. 831 Unusually rapid development of hypertrophic osteoarthropathy in a patient with subacute bacterial endocarditis was reported. 1411 Of interest was the development of an apparently identical condition in dogs with pulmonary diseases. 1850, 2064

Sarcoidosis. The subject of sarcoidosis continued to intrigue physicians and to call forth extensive literary efforts. Additional reviews of literature and summaries of hospital experiences tended to confirm the recognized clinical and pathologic features of this disease. ^{163, 451, 611, 1317, 2218} The most comprehensive of these, by Longcope and Freiman, ¹³¹⁷ summarized 100 original cases (including 30 autopsies) from The Johns Hopkins Hospital and the Massachusetts General Hospital. The riddle of etiology was discussed at length, in the papers above and in separate communications. Rostenberg concluded "that the tuberculous causation of sarcoidosis is a most unlikely one" and suggested that "the most likely cause is a new infectious agent." ¹⁸¹¹ However, Moschocowitz concluded that "evidence has been submitted that points clearly to the fact that sarcoidosis is the result of the invasion of the body by dead or avirulent tubercle bacilli." ¹⁸⁰⁴ To Jaques, sarcoidosis represented an altered capacity of the host to react to various antigens. ¹⁰⁶⁵

For the student of rheumatic disease, interest in sarcoidosis has centered around the bone lesions which affect the hands and feet in from 8 to 30% of the cases. ^{398, 1317, 738, 2218} Although some descriptions did not mention bone involvement, it was on rare occasions the central or presenting feature. ^{141, 163} Clinically, the hands may resemble an atypical form of rheumatoid arthritis, remarkable for the size of deformities, with little interference with function. X-rays showed

extensive cystic formations.

Of particular interest were reports indicating that joint manifestations and lesions of skeletal muscle may be features of sarcoidosis. Myers, Gottlieb, Mattman, Eckley and Chason presented exhaustive investigations of four patients with polyarthritis resembling rheumatic fever and with hilar lymphadenopathy, in whom muscle biopsies showed evidence of sarcoidosis. Erythema nodosum was present in three of the cases. The skeletal muscle lesions were noteworthy in that typical granulomas were readily demonstrated in routine muscle biopsies obtained at random in three cases. ¹⁵¹⁹ In a similar patient with erythema nodosum stimulating rheumatic fever, the diagnosis of sarcoidosis was established by lymph node biopsy and a positive Kveim test, but muscle biopsy was negative. ¹¹¹⁰ In 24 patients with sarcoidosis involving the skeletal muscle, muscular pain and

stiffness were present in four cases, muscular weakness and atrophy in five. 1080 In a patient who had experienced pain and recurrent swelling of the ankle for several months, bone removed at the time of arthrodesis showed typical lesions of sarcoid. "Sections of joint capsule and synovium revealed an increase in fibrous tissue elements and occasional 'hard tubercles.' Lymphocytes were rare and giant cells were not found." It was not possible to determine whether the cartilage was being invaded by the granuloma, or whether it was undergoing fibrous transformation without prior degradation. In another patient, the occurrence of polyarthritis and sarcoidosis was believed to represent the coincidental development of rheumatoid arthritis and sarcoidosis.

The Kveim reaction (intracutaneous injection of an antigen made from sarcoid lesions, with resultant papular reaction at the site of injection) was positive in 96% of cases, 480 although its usefulness as a diagnostic agent was limited because of the length of time it may take for the papules to develop.

Cortisone and ACTH were the only therapeutic agents of any significance. Their action was often prompt and dramatic, 1109, 1817, 1824, 1911, 1925, 1987 although the question has been raised as to whether they alter the final course of the disease. Pregnancy was reported as exerting a beneficial effect, 172 although others 540 reported no effect, good or bad. Of theoretic interest were observations that the negative tuberculin test in some patients with sarcoidosis could, under certain conditions, be converted temporarily to a positive reaction by cortisone. 1694

Osteochondritis. Osteochondritis of Growth Centers (Epiphysitis). Involvement of the hip by this disturbance in bone development is usually referred to by some variation of the name of Legg-Calvé-Perthes disease; some thought it would best be called "flat-headed femur." 1180 The importance of early recognition by roentgenography was again emphasized. 1917 Martin stressed the significance of the symmetry of the normal pelvis, the hips being "mirror images of each other." Alterations in the usual anatomic factors producing asymmetry can be accurately measured by tracing certain geometric patterns on x-rays. Appreciation of such alterations before demonstrable bony changes occur in the femoral head may point to the diagnosis. 1880 Kite and French suggested four alterations of the radiographic appearance that assist in early diagnosis: lateral displacement of the affected femoral head, decrease in size of the obturator foramen, alteration in shape of the head, and measurement of early bone atrophy by a photoelectric light meter. 1180

The essential principle of treatment was that elimination of weight-bearing begin 'as soon as the disease is suspected, and be discontinued only when clinical and x-ray findings do not substantiate the diagnosis." ¹⁹¹⁷ A recapitulation of late results of therapy in 78 hips of 72 patients indicated that ambulatory and nonambulatory forms of therapy were of about equal effectiveness, early institution of treatment being more important than the type used. ¹⁴⁷⁷ But in other hands, prolonged bed-rest and traction produced a "vastly improved end result" when compared to ambulatory treatment, with protection from weight-bearing by means of a crutch and contralateral shoe lift. ¹⁶⁸⁷ A combined method of therapy was described, using bed-rest and traction until degenerative changes stopped and regeneration began, and then shifting to a nonweight-bearing brace until regeneration was well advanced. ⁹⁴²

Osteochondritis of the foot bones accounted for the complaints of 13 of 1,232

children with foot problems. Localized osteochondritis of the spine 869 and of an accessory ossification center at the inferior pole of the patella 278 was the

subject of case reports.

Osteochondritis Dissecans. In a succinct summary of the generally accepted factors relating to this condition, Shipp pointed out that it occurs in joint surfaces which are exposed to trauma, and in which the articular blood supply may be barely sufficient for normal wear and tear. Hence, either repeated subclinical trauma or a single major injury to such a critical area may so interrupt the blood supply of the subchondral bone as to bring about necrosis. 1907 During the stage of necrosis, symptoms may be absent, or may take the form of mild, transient joint pain. Separation was believed to be almost always accompanied by pain on weight-bearing, followed by joint effusion. After detachment, symptoms were those of an internal derangement of the knee. 1907, 1946 In a series of 27 children in whom a total of 36 joints were involved, only four had acute symptoms; in 21 there had been intermittent difficulty of a mild degree, and two were asymptomatic.880 Although the knee was most commonly affected, other locations reported included the elbow, 830, 1384, 1498, 1815 the head of the ulna,2123 the ankle,830 and the interphalangeal joint of the thumb.1713 Some felt that the condition could be detected in its incipient stage and sequestration could be prevented by immobilization. 1559 In young persons, healing was often obtained by immobilization if separation had not occurred, but prompt surgery was the treatment of choice if separation of a loose body had occurred or was imminent.830, 1948 Others felt that early surgical intervention before separation of the sequestrum provided the best prognosis. 1907

Other Conditions. Bingold called attention to the fact that about one third of reported cases of skeletal neurofibromatosis have joint changes, consisting of dysplasias, sclerosis of articulating bone ends, or secondary osteoarthritis. Changes in the femoral head in children suffering from Gaucher's disease simulated Perthes disease; splenectomy did not appear to hasten or retard the development of bone involvement. In a patient with extensive aseptic necrosis of bone due to caisson disease, absence of joint symptoms was attributed to the fact that articulating cartilage had not been affected. Extensive primary calcification of articular cartilage was asymptomatic in one patient.

STRUCTURE AND FUNCTION OF ARTICULAR TISSUES

Fundamental Characteristics of Connective Tissue

Continued interest in the characteristics of connective tissue and its components was manifested in numerous reports. Valuable reviews summarized current concepts regarding the development and properties of cellular and fibrillar elements and of ground substance, with emphasis on the function of connective tissue. 1125, 1704 Problems encountered in such studies were discussed. The notion that the connective tissue is an inert stuffing material filling up the body spaces is giving way to the realization that the extracellular rissue "space" is constituted by fibrils and by a complex and potentially reactive gel, which acts as a filter-bed for nutrients and metabolites passing to and from cells and blood vessels. In turn, the properties of this tissue are sensitive to changes in its environment (Gross 149).

Fibrillar Elements. Collagen and Reticulin. Use of the electron microscope was extended from the study of isolated fibrils to direct examination of thin layers of tissue to obtain further information regarding the fibrillar structure in the natural state. A network of submicroscopic fibrils of 300 to 800 Å in width was found as a regular structure within the ground substance, with still smaller fiber threads, "protofibrils," between the fibrils. In general, the range in periodicity was the same as that previously reported for collagen (500 to 800 Å). Periods of less than 640 Å were relatively more frequent in the solitary fibril than in those from collagenous bundles. No marked difference in amount, diameter, structure or periodicity of units was found in very young or old animals, or in various diseases. 2200 While the fine structure of reticulin as revealed by the electron microscope was indistinguishable from that of collagen, 2133, 2200 the difference in staining properties between the two was used as the basis for general classification of supporting structures. 1292 It was pointed out that the problem may be one of purity, since reticulin seems always to be associated with a certain amount of collagen and ground substance; 848 some evidence supported the concept that the argyrophilia of reticulin may be an interface phenomenon occurring at the boundary between ground substance and fibril.2133 Structural variations in the appearance of collagen fibers under the electron microscope were induced by exposure to various chemical and enzymatic agents.848 Electron microscopy and x-ray diffraction technics were used in studies of collagen in various disease states, including various "collagen diseases." 722, 1126, 1745 [While these studies have not yet clearly defined the nature of the change in collagen in pathologic conditions, they have defined limiting conditions as a basis for further studies.-Ed.]

The locus of collagen fibril formation remained controversial. The collagen of certain forms of connective tissue could be dissolved in organic acid buffers and then reconstituted as fibrils by dialysis. The fine structure of the reconstituted fibrils varied with the conditions of the experiments. Mucoprotein was found to induce the precipitation of fibrils, some of which had the characteristics of typical collagen; 961 however, a variety of organic substances appeared to have similar properties, and the action of these precipitating substances seemed to be nonspecific.850, 1499 The solubility of precollagen from rabbit skin was not significantly affected by acid mucopolysaccharides. 2212 Investigations using biochemical methods for characterizing collagen established that ascorbic acid was not required for the maintenance of established or newly formed collagen. 1764, 1765 However, the need for ascorbic acid in the formation of collagen was unequivocally demonstrated; possibly it is necessary for the formation of collagen fibers from a collagen precursor. 1767 Alkaline phosphatase did not appear to play a role in fiber formation. The association of phosphatase activity with fibrogenesis in healing wounds was attributed to adsorption of the enzyme from surrounding tissue fluids on the newly formed fiber in sufficient concentration to be visualized by histochemical methods.777, 809

By the feeding to rats of glycine labeled with C14, the metabolic activity of collagen could be compared with that of other tissue proteins in terms of both rate of uptake and turnover of the isotope. Collagen from liver, bone, skin and tendon was much less active than muscle or liver protein. In young animals there appeared to be a significant uptake and turnover in collagen. But when correction was made for newly formed collagen in the process of growth, collagen was found to be relatively inert metabolically, even in young animals. 1542, 1548 The results of similar studies

in normal and scorbutic guinea pigs suggested that labeled amino acids may get into collagen without complete resynthesis of the macromolecule.¹⁷⁶⁶

The x-ray diffraction pattern of collagen has been sufficiently well characterized to permit attempts to describe its precise molecular configuration. One proposed structure consisted of three poplypeptide chains with a specific sequence of amide linkages, each chain being coiled, and with the three helical chains around a common axis. 1610 X-ray diffraction analyses of rat-tail tendons soaked in solutions where hydroxy-apatite was being formed indicated that collagen in some way oriented the mineral salts. 616 The ratio of collagen to hexosamine of the skin increased with increasing age. 1972 Water exchange and hydrophilic properties of dense collagenous tissue differed in some respects from those of gelatin [denatured collagen—Ed.]. 1884 Further progress in preparation of specific collagenase free of other proteinases from Clostridium histolyticum was reported. 1356

Elastic Fibers. The preparation and chemical characterization of elastin was standardized. Study of elastic fibers exposed to elastase revealed four fibrils, each $1\,\mu$ in diameter, which formed two pairs of mutually intertwined strands embedded in matrix. The presence of elementary threads 25 m μ in diameter, which aggregated by twisting to form fibrils, was established.¹²³⁶ The coiled threads previously described after digestion of elastic fibers with trypsin were shown to arise from bacterial contaminants of the trypsin.^{678, 647}

Ground Substance. The ground substance was defined as the extracellular, extrafibrillar amorphous matrix, which varies in content from tissue to tissue. The matrix consists of water, salts, nonelectrolytes, proteins, mucoproteins, mucopolysaccharides and other substances, which are all probably in various states of interaction with each other. The mucoprotein-polysaccharide complex of ground substance has been the subject of intensive investigation by histochemical means and by isolation technics. Histochemical methods are admittedly crude and often nonspecific. With isolation technics, exact localization of the tissue extracted is impossible, and during the process of extraction the material is denatured, degraded or depolymerized to a certain extent. Knowledge concerning the components of ground substance was reviewed. Knowledge concerning the components of ground substance was reviewed.

Limitations of histochemical methods were emphasized by demonstration of competition between dye and protein when mucopolysaccharides were stained with basic dyes, such as toluidine blue. The loss of staining after the tissue had been subjected to enzymes such as hyaluronidase did not establish specificity, since this effect could be produced by destruction of attached protein or by masking of the staining group by protein, as well as by action of a specific depolymerase. Such studies "clearly indicate the need for caution in the use of and more particularly in the interpretation of the results obtained following the application of impure hydrolytic enzymes to tissue sections" (Benditt and French 151). [We heartily agree.—Ed.]

On the basis of affinity for colloidal iron, acid mucopolysaccharide was demonstrated in subepidermal connective tissue, on glomerular basement membrane, in renal pyramids and in intima of arteries. 1786 [The method is not specific for identification.—Ed.] Unfixed skin collagen became metachromatic when treated with pepsin but not with trypsin, whereas denatured collagen became metachromatic with either. 1669 [The conclusion that pepsin attacked the protein of a protein-polysaccharide complex and freed groups of the polysaccharide which combined with the dye is hypothetic.—Ed.] Unusual persistence of metachromatic ground substance was noted during study of regeneration of tendon. 298 Metachromasia was found in the tendons of guinea pigs, especially in the

chondroid part near the insertion. The staining did not change after prolonged exercise, but the glucosamine and sulfur contents of the tendons were higher in exercised animals than in the controls.²²⁹⁸

On the basis of extraction and isolation, Meyer and Rapport distinguished five mucopolysaccharides in connective tissue: (1) hyaluronic acid in vitreous humor, synovial fluid, skin and umbilical cord; (2) chondroitin sulfate A in hyaline cartilage; (3) chondroitin sulfate B in heart valves, tendon, aorta and skin; (4) chondroitin sulfate C in hyaline cartilage, heart valves, tendon, aorta and umbilical cord; and (5) hyaluronosulfate in cornea.1458 The predominant polysaccharides of subcutaneous tissues were found to be rich in galactose and in glucosamine. 420 The interfibrillary substance was visualized as a microfabric of protein molecules "water-proofed" by molecules of hyaluronic acid. This concept was developed on the basis of studies of the flow of saline through connective tissue membrane, which was markedly increased by hyaluronidase; this effect was reversed by perfusion with starch or dextran. 498 Exposure to x-ray irradiation appeared to alter the polysaccharide component of connective tissue.⁵⁷⁹ Injection of thyrotropin in either thyroidectomized or normal guinea pigs caused accumulation of mast cells and hyaluronidase-sensitive polysaccharide in the retrobulbar tissues. 70 [The conclusion that the polysaccharide might bind more water and cause protrusion of the eyes was not based on any real evidence.-Ed.]

Hyaluronic Acid. It was demonstrated that glucose labeled with C¹⁴ was incorporated without breakdown into 3-carbon fragments into both the glucosamine and glucuronic acid moieties of hyaluronic acid by certain strains of Group A steptococcus. ^{1797, 1798} [This is one of the first studies dealing with the biosynthesis of hyaluronic acid. —Ed.] A crystalline disaccharide with the structure of a glucuronido-glucosamine was isolated from hyaluronic acid after acid hydrolysis, with or without previous hydrolysis with testicular hydraluronidase; it was named "hyalobiuronic acid." ^{1721, 2228} Chromatograms of acid-hydrolyzed hyaluronate from umbilical cords showed presence of d-glucosamine and a uronic acid. ¹¹¹⁴ A method for methylation of hyaluronic acid was described which yielded 75% of an undegraded product in which three and one-half of four hydroxyl groups were methylated. ²⁰⁷⁰ Further suggestion that synovial cells in tissue culture produce hyaluronic acid was obtained by Kulonen, who observed that the turbidity of the culture solution which resulted from acidification could be reduced by incubation with testicular hyaluronidase. ¹²⁰⁹

Detailed study of the alleged metachromasia of hyaluronic acid indicated that this property depended on the physical state and concentration of the polysaccharide. It was concluded that "metachromatic staining reaction for the demonstration of hyaluronic acid is of little value." ²⁰⁸⁹ Hyaluronate in supernatant fluid after centrifugation of vitreous humor was found to be an active thromboplastic agent; the activity was related to its viscosity. The water and electrolyte binding properties of the polysaccharide varied with the degree of its polymerization. Exposure to x-rays reduced the viscosity of hyaluronate obtained from vitreous humor and umbilical cord, and altered the rate of hyaluronidase action. Other studies on hyaluronic acid are included below in the section on Synovial Fluid.—Ed.]

Chondroitin Sulfate. Improved extraction procedures and further studies of physical properties were reported. Studies of viscosity and cation binding indicated that chondroitin sulfate behaved as a linear polyelectrolyte, with molecular configuration depending on the ionic environment.¹³⁹⁴, ¹³⁹⁵ [Studies on chondroitin sulfate in cartilage are included in the section on Physiology of Cartilage.—Ed.]

Hyaluronidase. Comprehensive reviews of the occurrence and characteristics of the enzymes which depolymerize and hydrolyze hyaluronic acid were presented by Meyer and Rapport 1454 and by Kulonen. The mucin clot-prevention method of assay was found suitable for detection of the enzyme in small concentrations, and was used as a rapid test for many purposes. 1454, 2194 The turbidimetric method was further

studied with special reference to the influence of sodium chloride on enzyme activity at various hydrogen ion concentrations, the necessity for stabilization of the enzyme, and the factors influencing the production of turbidity.^{22, 168} The turbidimetric method was found superior to the viscosity-reducing method, since it was more nearly independent of the state of the substrate. The reductimetric method was preferable for kinetic studies. The desirability of standardization of procedures to facilitate comparison of results among different laboratories was emphasized.¹⁵⁵⁴ Colorimetric methods were described, using Bromosulphalein ⁸³⁶ and hemoglobin ¹⁶⁵¹ as indicators of the measurement of amount of protein co-precipitated with the hyaluronate in acid solution. [These methods will require further evaluation.—Ed.] A turbidimetric method for assay of the chondroitinase activity of testicular hyaluronidase was described.¹³⁹⁶

Further studies of the mechanism of hyaluronate degradation indicated that no monosaccharides were liberated by pneumococcal or by purified testicular hyaluronidases. The differences in ratios of acetylglucosamine to reducing sugar produced by the two enzymes were explained by the hypothesis that there are two types of acetylglucosaminidic linkages, only one of which was hydrolyzed by the testicular enzyme, while the pneumococcal enzyme hydrolyzed both. Tip, Tipo Crude testicular extracts were shown to contain a beta-glucuronidase which hydrolyzed to monosaccharides the oligosaccharides resulting from the action of purified testicular hyaluronidase. The differences between streptococcal and other bacterial hyaluronidases and testicular hyaluronidase were summarized. Elevated sedimentation rates were not lowered by bacterial hyaluronidase.

It was again emphasized that hyaluronidase preparations are really mixtures of several hydrolytic enzymes. The constancy of the ratios of the chondroitinase and the hyaluronidase activities of testicular preparations over a wide range of purities, as well as similar action of inhibitors of enzyme action on either substrate, made it highly probable that a single enzyme depolymerized both chondroitin sulfuric acid and hyaluronic acid. The ability of crude testicular extract to increase capillary permeability was lost during purification of the hyaluronidase component. 152, 1912

Hyaluronidase Inhibitors. "The literature on inhibition and inactivation of hyaluronidase has become very voluminous and confusing" (Meyer and Rapport 1454). Interest centered particularly on the nonspecific inhibitors present in serum; the level of such inhibitors has been found elevated in patients with a variety of diseases, including some of the rheumatic diseases. The Some workers found no correlation of the serum level with age and sex, The while others found the values slightly higher in women between the ages of 30 and 60 years. Variations observed in the concentrations of hyaluronidase inhibitor and of mucoproteins in maternal and infant serum did not show a consistent relationship between the two. The Approximately 15% of the inhibiting capacity of plasma was found to be thermolabile.

The level of nonspecific inhibitor was unchanged by immunization or anaphylactic shock, but was increased in rabbits with Arthus' or Shwartzman reactions or serum sickness. In normal animals the level rose with exposure to cold, repeated stress, or after ACTH or cortisone treatment, but in adrenalectomized animals there was no rise with exposure to cold.^{766, 799} The results were interpreted as indicating a possible adrenal cortical regulatory effect on the serum level of the inhibitor. [There is too little evidence to support such a hypothesis.—Ed.] Cortisone did not alter the increase in serum inhibitor that followed surgical wounding in dogs.³⁹⁵ Inhibitors of bacterial hyaluronidases with characteristics of specific antibodies were also extensively studied.¹⁶⁸

Methods for purification of the nonspecific inhibitor were described by Wattenberg and Glick. The increased concentration of metachromatic material with purification suggested to them the presence of an acid polysaccharide, possibly heparin. [Such evidence is not reliable for identification.—Ed.] Eighty-five per cent of the purified inhibitor migrated as one component with a mobility like that of albumin, the remainder having a slower mobility in the range of alpha-globulin. The purified material was found to contain caeruloplasmin, but the concentration of this protein did not parallel the inhibitor activity.²²¹⁰ In dogs in which the liver was excluded by operation the nonspecific inhibitor level fell progressively until death, suggesting a major role of the liver in its production.⁵⁹⁴ Proteolytic enzymes and snake venom restored hyaluronidase activity after its inhibition by serum.⁸⁶⁵ This nonspecific inhibitor was believed to combine with hyaluronidase to form an inactive complex; this effect of the inhibitor could be reversed by colloidal iron and prevented by toluidine blue.¹²¹⁰

Ferric, cupric, ferrous and zinc salts were also found to inhibit testicular hyaluronidase. Apparently the hyaluronidase combined reversibly with these ions and the enzyme inhibition could be prevented or reversed by a number of compounds which form a metal complex. Ascorbic acid caused slight inhibition of hyaluronidase in vitro. The Homogentisic acid and pure gentisic acid did not inhibit testicular hyaluronidase in vitro, but crude gentisic acid, quinones and "humic acid" from benzoquinone did. The Homogentisic acid.

In rabbits a parallel was found between the increase in hyaluronidase inhibitor and the increase in heparin produced by peptone shock and, to a lesser degree, by desoxy-corticosterone acetate, though the magnitude and time of change varied. A general correlation was observed between the anti-inhibitor effects of various dyes and their reported antiheparin actions. Tissues rich in mast cells were found to contain hyaluronidase inhibitor roughly proportional in activity to the heparin content of the tissues. Intravenous injection of heparin inhibited the spreading action of hyaluronidase. Intravenous injection of heparin inhibition of hyaluronidase by heparin, soff and antihistamines did not alter the inhibition of hyaluronidase. Ascorbic acid was reported to inhibit hyaluronidase in both the test tube and the experimental animai. Issues are considered to inhibit hyaluronidase in both the test tube and the experimental animai. Issues are summarized in the sections on Rheumatic Fever and on Rheumatic Diseases and the Adrenal Cortex.—Ed.]

Synovial Tissues and Synovial Fluid

Anatomy. The present knowledge of the blood and nerve supply to joints was summarized by Gardner. He noted the variation in the manner in which nerves reach the joints, the overlapping so that each major region of a joint is supplied by at least two articular nerves, and the presence in articular nerves of both myelinated and nonmyelinated fibers which form various kinds of endings in the joints. The larger fibers, which give rise to proprioceptive endings, and the pain fibers have multiple pathways in the spinal cord and brain.⁷²⁸

Joint Fluid. The hyaluronic acid component was again demonstrated to play an important part in determining the lubricant properties of synovial fluid under both dynamic and static conditions. Ogston and Stanier studied ox synovial fluid with respect to its viscosity and its resistance to flow in thin films. They found it to have a special capacity for forming a layer which has a considerable resistance to static compression and which has some degree of elasticity. The viscosity was strongly dependent on the concentration of mucopolysaccharide, and decreased with increasing velocity gradients (non-Newtonian character of viscosity). Since joint structure is such that the articulating surfaces act as

"slipper bearings," the drag of such a bearing and the load it will support were both thought to be dependent on the product of the viscosity of the fluid and the rate of movement. "A solution of hyaluronic acid is peculiarly suitable for lubricating a bearing of this type, required to carry a load at varying rate of movement. The viscosity is very high at lowest rates of shear, so that the joint is enabled to support a high load even at low rates of movement. At higher rates of movement, viscosity falls so that the drag of the joint is relatively lessened; the load which it will bear is not reduced, because the greater rate of movement more than offsets the fall in viscosity. A Newtonian fluid would not give these advantages. Furthermore, hyaluronic acid produces a high viscosity at a low concentration, without any large osmotic effect such as would be produced, for example, by protein at a concentration needed to give a similar viscosity. The properties of hyaluronic acid result from its high molecular weight and its random-chained structure." 1875

Further information regarding the state of the naturally occurring polysaccharide resulted from studies of viscosity in relation to concentration and from analysis of degradation rates by testicular hyaluronidase. Sundblad used a method for estimating hyaluronic acid content based on determination of the hexosamine moiety, and calculated values for intrinsic viscosity from a single determination of relative viscosity. The viscosimetric behavior was similar in normal and pathologic synovial fluids and in solutions of pure hyaluronate, and supported the view that the higher viscosity per unit of polysaccharide concentration in normal synovial fluid could be attributed entirely to higher mean polymerization of the naturally occurring polysaccharide. 2067, 2068 Ogston and Stanier continued to find ultrafiltration the best method of isolating the polysaccharide complex with a minimum of degradation, and confirmed their previous finding that the protein content of the complex is not reduced below a limiting value of 25% during purification. 1574 Viscosity and streaming birefringence measurements were consistent with the hypothesis that the particle of hyaluronic acid complex has a weight of 8×10^6 (with axial ratio of the order 1), is nearly spherical and is very highly solvated. These properties were consistent with the view that hyaluronic acid complex is a flexible chain, and that variation of viscosity with velocity gradient can be explained in terms of interaction between particles. 1578 Depolymerization of hyaluronic acid of synovial fluid produced no significant change in the freezing point. 1209 On the basis of studies of metachromasia, Hammerman and Schubert concluded that the polysaccharide of synovial fluid in the native state is bound and that its anionic groups are not entirely free. Synovial fluid was not metachromatic with methylene blue but could be made so by adding sulfur-free hyaluronate or by addition of alkali. The metachromasia of sulfur-free hyaluronate could be inhibited by addition of egg albumin or gelatin.885

The literature on cytologic findings in normal animal and human joints was summarized. 1005 The concentration of hyaluronic acid in normal human fluid was found to be 0.2 to 0.4 gm. per 100 ml. The values obtained on horse and calf fluid were slightly lower. 2087, 2068 The protein content of normal animal and human fluids ranged from 1 to 3 gm. per 100 ml. 1581, 2067, 2068

Ogston and Stanier believed that principles derived from studies on degradation of normal synovial fluid can be applied to studies on fluids obtained from diseased joints, and that the degree of degradation of hyaluronic acid in pathologic synovial fluids can be estimated by comparing the viscosity, measured under standard conditions, with that of normal joint fluid with the same polysaccharide concentration.¹⁵⁷⁶ Sundblad used essentially the same principles in calculating

intrinsic viscosity, which he found to be more helpful than relative viscosity or hyaluronic acid concentration in differentiating the inflammatory effusions from those of traumatic disorders or degenerative joint disease. However, Kulonen found the relative viscosity to be helpful in this differentiation. The protein concentration in synovial fluid was also found to be higher in inflammatory synovial fluids. In rheumatoid effusions of long duration there were little or no fibrinogen and remarkably high concentration of gamma-globulin. The freezing points of two trauma fluids were -0.550 and $-0.607\,^{\circ}$ C., while those of chronic effusions ranged from -0.625 to $-0.655\,^{\circ}$ C.

Physiology. Vasodilator and vasoconstrictor drugs did not appreciably modify the temperature in diseased joints. Much more significant changes could be induced by physical means and by action of ACTH, cortisone and intra-articular hydrocortisone. Whyte and Reader recorded intra-articular and skin temperature alterations produced by applying various forms of heat to the knee. Diathermy was more effective in raising the joint temperature than was infrared radiation. The effect of radiant heat on the joint was thought to be determined mainly by changes produced in the whole limb. 2241 Blood flow through the knee segment was determined by venous occlusion plethysmography; it was estimated that 55% of blood in the normal knee segment represented flow through the bones and the joint. 227

When radioactive sodium was injected into the knee joints of 35 normal subjects, it disappeared at a slower rate than that observed following subcutaneous or intramuscular injection. The rate of clearance was more rapid in women than in men, and among women the most rapid clearance appeared to occur during the early phase of the menstrual cycle. This suggested a hormonal control of synovial permeability. 1060 [Much more evidence would be necessary to establish such a theory.-Ed.] Further studies of synovial permeability to phenolsulfonphthalein in normal rabbits and in patients indicated that this function was not significantly altered by systemic administration of cortisone, corticotropin or adrenal cortical extract.957, 1618 When synovial permeability was increased by intra-articular injection of hyaluronidase, some workers noted that this effect was inhibited by corticotropin.987 Others noted no significant alteration in permeability after injection of hyaluronidase into the joint. 1618 Injection of hyaluronidase into the joints of normal dogs was followed by a substantial increase in the concentration of sodium and potassium in the synovial fluid. 2297 The resistance to flow through synovial membrane in rabbits in whom the joints were made hydropic by induced pericarditis showed no "breaking point," and was not influenced by a mercurial diuretic; behavior paralleled observations previously reported in inflammatory edema of the synovium. 583

Study of the interaction of ions and tissue indicated a high concentration of negatively charged immobile colloid in the unrelaxed pubic symphyses of guinea pigs; there was a low concentration of such ions after relaxation during pregnancy. In the relaxed symphyses the mobility of cations approached that in water, whereas in tight symphyses, selective effects appeared. Similar results were obtained with relaxin administration. Systemic administration of cortisone reduced the effects of glucosamine and aminopurines on the joint potential in dogs. In 1954 Reed and Day reported that many of the potential changes which they had noted in synovial tissues were induced by the use of stainless steel needles. They questioned whether synovial potentials are in any way directly related to the metabolic activity of synovial tissues.—Ed.]

Physiology of Cartilage. On the basis of microscopic studies, MacConaill found the amount of collagen in hyaline cartilage to be greater than is commonly

supposed; the density of the fibrous material was distributed in accordance with the customary stresses on the part. 1349 Procedures were developed for analysis of water, electrolytes, total and collagen nitrogen, and of chondroitin sulfate in articular cartilage. The fiber solids and chondroitin sulfate were found to comprise 68% of the solids. Fresh cartilage (1,000 gm.) was considered to be composed of two compartments: extracellular (662 gm. with 161 gm. solids), and intracellular (338 gm. with 74 gm. solids). 599 The concentration of chondroitin sulfate in new cartilage was found to be 5.8%, a lower concentration than usually reported.⁵⁷¹ The content of chondroitin sulfate was greater and that of collagen was less in weight-bearing articular cartilage, as compared with cartilage that bears no weight. 1398 [The conclusion that the higher polysaccharide content provides greater resilience is hypothetic.—Ed.] From the chemical composition of cartilage of joint surfaces of poliomyelitis patients, it was estimated that the proportion of chondroitin sulfate solids to connective tissue solids was decreased. It was thought that the decrease in the chondroitin sulfate phase was related partly to the effect of age and partly to the duration of the paralysis. 600 [The validity of some of the assumptions used in deriving the data in this study was not proved.—Ed.] Chondroitin sulfate extracted from cartilage with calcium chloride was found to contain firmly bound protein that could not be removed with a mixture of amyl alcohol and chloroform. The amino acid pattern of the protein with a high proline and hydroxyproline content was compatible with that of gelatin. 1270 A method for comparing the area of glycogen staining in cartilage slices with extent of inorganic salt deposition was described by Marks and Shorr. The removal of glycogen from cartilage slices was found to interfere markedly with the deposition of calcium or strontium. 1871

The problem of the nutrition of articular cartilage was extensively investigated by Swedish workers. The thickness of articular cartilage was found to increase with nonweight-bearing exercises, the increase being greater in patients with arthritis deformans than in normal subjects, but less than normal in patients with "rheumatic polyarthritis." 1000, 1042 Ingelmark concluded that much of the fluid entering the cartilage came from synovial fluid, but that some came from the medullary cavities of bone. 1042 Ekholm found some selective localization of radioactive gold in tibial and femoral cartilage after it was injected into the tibial epiphysis in rabbits. He concluded that part of the nutrition of cartilage came from the medullary spaces and part from synovial fluid, and that the nutrition was improved by function. 602 Two types of direct contacts between cartilage and medullary cavity, wide contacts and canal-like ones, were demonstrated.1001 The area of such contacts was often only 1%, but occasionally amounted to 7%, of the total area of cartilage in contact with underlying bone. Usually it was the calcified portion of articular cartilage that was in contact with the medullary cavity, but in isolated cases, offshoots of medullary cavity tissue extended into uncalcified cartilage. 1001, 1042 The volume of synovial fluid in rabbit joints was also found to increase after exercise, the increase being associated with a lower concentration of protein and of hyaluronic acid. 608

Radioactive sulfur (S³5) was used to study factors influencing the chondroitin sulfate in cartilage. Labeled chondroitin sulfate was isolated from rib cartilage 238 and from articular cartilage 570 and specific activity determined at intervals after the intraperitoneal injection of S³5-labeled sodium sulfate in rats. With this procedure,

labeled sulfate was shown to be deposited in articular cartilage in 15 minutes, the concentration being highest at the epiphyseal-diaphyseal junction. The S³5 was presumably incorporated into the chondroitin sulfate of the cartilage. Sulfur³5, in a form insoluble as barium salt, was found in centers of secondary ossification and bone marrow and bone shaft, with highest concentration in 24 hours. 572, 578 Pretreatment with thiouracil decreased the uptake of S³5 by the articular cartilage, and thyroxine caused a decrease or no change. Thiouracil decreased the rate at which the S³5 concentration diminished, whereas thyroxine accelerated this process. 571 An exchange of S³5-labeled sulfate with the sulfur of chondroitin sulfate was demonstrated in cartilage slices in vitro; this appeared to be an enzymatic reaction. 539 [These methods do not permit differentiating simple exchange of S³6 with unlabeled sulfur in already formed chondroitin sulfate from incorporation of the S³6 into newly formed mucopolysaccharide.—Ed.]

Costal cartilage from persons ranging in age from premature infants to 89 years was examined by histochemical and chemical methods. Evidence was obtained that both the cartilage content of chondroitin sulfate and the degree of polymerization of the polysaccharide decreased with increasing age. It was suggested the depolymerization of chondroitin sulfate may be a factor in the calcification of cartilage, since this would increase the number of side chains available for acceptance of calcium ions. Study of the changes in the femoral head underlying a vitallium cup showed no cartilage in a woman of 63 who had walked very little for one year after arthroplasty, whereas true articular cartilage covered the femoral head in a man of 38 who had been active for three years and eight months after operation. It was concluded that compression and gliding movement were necessary to reproduce cartilage. There is not adequate evidence to support such a conclusion.—Ed.]

Development of Articular Structures. Gardner summarized his observations on the prenatal development of human joints, indicating that initial development is rapid. A form and arrangement resembling those of the adult are reached by approximately the seventh week of intra-uterine life. The total time from the first indication of joint formation to a state where all eventual components are represented may take no more than a few days. No phylogenetic recapitulation was noted. Development of a joint cavity does not begin until initial articular form is well established; but once cavitation begins it proceeds rapidly, and in a short time there is evidence of a lining structure similar to the adult synovium.⁷²⁷ The prenatal development of the elbow joint,⁸²¹ the shoulder and acromioclavicular joints,⁷²⁹ and the knee joint ⁸⁷⁵ was described in detail. Information was added regarding the manner in which the fibula is excluded from the knee joint during development.¹⁵⁸⁰

Joint Motion and Joint Pain. An excellent study emphasized that the characteristics of joint movement reflect the characteristics of synovial fluid; this was demonstrated by measurement of the rate of shear in ratio to the force applied to cat joints. Serial x-ray studies demonstrated that movement of the finger and knee joints is essentially a gliding motion. The effect of chilling in slowing up joint motion was attributed to the increased viscosity of the joint fluid at lower temperatures. Since the fall in temperature in the joint on exposure to cold is greater than that in muscle or skin, the accompanying increase in fluid viscosity results in an increase in resistance to joint motion and a decrease in the maximal speed at which the joints can be moved. It was observed that equivalent slowing of the speed of motion of the fingers was obtained by application of cold to the fingers, to the wrist and to the elbow. 1030, 1081

In the temporomandibular joint, the meniscus was found to be firmly attached to the base of the skull on the posterior, lateral and medial edges. The meniscus does not move as the jaw opens and closes, as has been generally accepted. The amplitude of forearm and humeral rotations was measured critically. Sometric analysis indicated that all motions of the joints of the foot, excluding the toes, were axial rotations. A plastic goniometer with extensible arms and a detenting device that fixes the arms without danger of slipping was described. A method of determining the angle of a joint in order to evaluate a change in range of motion was described. Equal distances were measured on both sides of the joint and the hypotenuse of the equilateral triangle thus formed was determined. Preliminary studies suggested that direct auscultation might permit differentiation of the sounds produced on motion of normal and of diseased joints.

The various qualities of pain and their origins were discussed. The pricking, burning pain from superficial tissues, including joints, is well localized and rarely produces muscular rigidity. The deep, aching pain from deep structures, including muscles, tendons, deep joints and bone, is often of segmental distribution and associated with muscle spasm and systemic reactions. The criteria of value in recognizing pain which is predominantly psychogenic were discussed. 380

EXPERIMENTAL ARTHRITIS

Chemical "Arthritis." Interest centered on the inflammation produced by injection of formaldehyde solutions into the plantar foot pads of rats. Careful histologic studies showed that this inflammation was periarticular and did not extend into the joint itself, although the presence of a granular precipitate in the joint cavity and an increase in solid matter in the synovial fluid suggested an increased permeability of synovial tissues. A similar precipitate was seen in the joint cavity in the opposite paw. By one week after injection the synovial fluid and membranes had returned to normal, although periarticular infiltration and fibroblastic reaction in some animals persisted more than a month. By the time of onset of cellular infiltration around the joints, eight hours after formalin injection, the adrenal cortex showed extensive loss of lipoids.247 In animals treated with DOCA, the inflammatory infiltration and fiber production were more pronounced and penetrated into the joint itself. With ACTH treatment, there was no loss of lipoids from the adrenal cortex.248 The inflammatory reaction was less severe in young rats. Exposure to cold increased the swelling, especially in young rats.561

The reported effects of various agents on the "arthritis" produced by formaldehyde continued to show many inconsistencies. In normal rats cortisone and ACTH were found to have no significant effect, 248, 1804 or to lessen the swelling. 854 In adrenalectomized rats, cortisone and ACTH reduced the swelling, as did also epinephrine, aminopterin, sodium salicylate and betanaphthyl salicylate. 854 DOCA and DOCA plus ascorbic acid increased the swelling in normal rats. 85, 248, 1804 No difference was found between the adrenalectomized animals treated with DOCA and those with DOCA plus ascorbic acid. 806 Ascorbic acid alone decreased the swelling in the experiments of Bacchus, 81 but was effective only in old rats in the studies of Dugal. 861 In adrenalectomized rats, ascorbic acid had no effect on the swelling. 81, 82 [Any attempt to interpret the significance of the effect of drugs in the "arthritis" produced by formaldehyde would be premature until more consistent results have been obtained.—Ed.]

Arthritis Induced by Microorganisms. Histologic study of the joints of rats infected with pleuropneumonia-like organisms showed purulent lesions, largely periarticular in nature, but occasionally accompanied by destruction of cartilage. No consistent resemblance to any of the human rheumatic diseases was found. Since the disease tended to resolve spontaneously, Parkes and Wrigley concluded that prevention and cure of this disease could not be used as a valid screening test for substances thought to be useful in the treatment of rheumatic diseases. 1805 Many drugs have been tested for their preventive and curative effects in the polyarthritis of rats produced by pleuropneumonia-like organisms. Earlier work in this field was summarized by Kuzell. 1220 No additional drugs were found to have preventive or curative effects equal to those of gold, Aureomycin or Terramycin. ACTH and glutathione were again shown to have an adverse effect when used as preventives, and hydrocortisone was of no value in prevention or cure. Thymectomy was found to worsen the joint involvement slightly. Hypophysectomized animals died within 24 hours after infection. 1221, 1364 [There is no indication that the results in prevention or cure of the arthritis produced in rats by pleuropneumonia-like organisms can in any way be transposed to the treatment of rheumatoid arthritis.—Ed.] Sensitivity studies on 28 strains of pleuropneumonia-like organisms of human origin showed the majority of the strains to be sensitive to Aureomycin, chloramphenical and Terramycin, the latter being more effective in most instances.1774

A polyarthritis was produced in rats and mice by intravenous injection of an organism resembling Corynebacterium kutscheri. The joints showed thickening and proliferation of the synovial tissues, a fibrinopurulent exudate and destruction of articular surfaces. Polyarthritis was produced in rats and mice also by intravenous injection of alpha type streptococcus. Cortisone in doses of 15 mg. per kilogram increased the mortality and the incidence of arthritis in mice with this infection. Certain viruses were found to produce a nonspecific synovitis only when injected into the joints of rabbits; localization of the virus in the joint after intravenous or intratesticular injection was not produced by exposure of the synovium to trauma or to various streptococcal growth products. Prof. Injection into guinea pigs of emulsions of homologous joint and kidney tissue plus streptococci failed to produce any antibodies, urinary changes or histologic changes in the joints, kidney or heart.

Arthritis in calves due to Erysipelothrix rhusiopathiae was reported, reputedly for the first time. It was characterized by a proliferative synovitis with fluid formation, and diffuse and focal polymorphonuclear and mononuclear cell infiltration with prominent focal collections of lymphocytes. 1506 [The spontaneous occurrence in swine of arthritis due to infection with this organism is well recognized. It has also been reported in

lambs accidentally infected by contaminated vaccine.-Ed.]

Scurvy. In guinea pigs maintained on a diet free from ascorbic acid, there was no evidence that cortisone modified the progress of events in any way. It did not alter the scorbutic lesions if given after they had developed, and did modify the reparative processes when scorbutic animals were treated with ascorbic acid. The histologic studies demonstrated that matrix formation of epiphyseal cartilage ceased promptly as a result of ascorbic acid deficiency, with associated changes in the shape of the cartilage cells and great distortion of the cartilage cell columns. Restoration of apparently mature cartilage cells in normal columnar arrangement had taken place after three to four days of ascorbic acid therapy. Deposition of collagen in fibrous tissue and of osteoid in callus

formation and resumption of bone growth also occurred promptly. The changes in the adrenal in the scorbutic animals, similar to those produced by excessive administration of vitamin A and by acute inanition, were not altered by cortisone administration.²²⁷⁷ The concentration of glycoproteins in the serum, as reflected by the galactose-mannose and tyrosine concentrations, was found to be significantly elevated in acute and chronic scurvy in guinea pigs. This finding was interpreted as support for the theory that scurvy involves a depolymerization of carbohydrate-containing constituents of the ground substance of connective tissue.¹⁶⁶¹ [Such a conclusion is not warranted by the data presented.—Ed.]

Other Forms of Experimental Arthritis. When female rats were placed in parabiosis, arthritis frequently developed. Sodium chloride or unilateral nephrectomy did not potentiate the arthritis, and it was not confined to rats which developed hypertension. Despite these findings, Hall and Hall 879 suggested that the arthritis might be due to adrenal hyperactivity with hypersecretion of mineralo-corticoids. [The reported observations do not support this hypothesis.—Ed.]

[Arthritis produced by administration of desoxycorticosterone and of growth hormone is

discussed in the section on The Adrenal Cortex and Rheumatic Disease.-Ed.]

THE CAMPAIGN AGAINST RHEUMATISM

Interest in the rheumatic diseases has been steadily growing all over the world. This is manifested by the increasing number of members in the organizations for the study of these diseases in the different countries; in the greater number and high quality of scientific reports on arthritis; in the recognition of these diseases as a major cause of disability by public health agencies; and in the progressively greater sums available for improvement of facilities for care and research from foundations, individual donations and public funds. The great progress made in the international attack against rheumatism has been summarized by individuals with first-hand knowledge of this movement. 30, 83, 429, 566, 586, 788, 783, 2122

The enormous economic and social importance of the rheumatic disorders is beginning to receive the attention of local, national and international public health organizations. Determination of the prevalence of these crippling diseases has been the aim of several population surveys, in the U.S.A., 2290 Denmark, 37 England 1131 and Sweden. 213 Although the methods of study have varied, the prevalence in adults was found to represent approximately 18% of the population. The World Health Organization has recognized the rheumatic diseases as an international health problem and established a nine-member W.H.O. Expert Committee on Rheumatic Diseases. [The first committee report, published in 1954, reviewed these diseases from a public health standpoint, and emphasized the need for a uniform classification for the group of diseases termed "rheumatic" as a basis for surveys of incidence and prevalence which would be comparable from country to country. The report also stated that it is essential that adequate treatment facilities and hospital beds be made available; that general practitioners be better informed concerning management of rheumatic diseases; that research be encouraged; and that more attention be given to rehabilitation and to health education of the public to correct the erroneous belief that these diseases are incurable, practically untreatable and usually disabling .- Ed.]

La Ligue Internationale Contre le Rheumatisme, since its establishment in 1928, has been a unifying force in the development of rheumatology throughout

the world. The League came into existence at the time of the annual meeting of the International Society of Medical Hydrology in Buxton, England, with Dr. Fortescue Fox of London as President and Dr. J. Van Breemen of Amsterdam as Honorary Secretary.²¹²² It has among its aims the establishment of national committees for the promotion of scientific research, and the exchange of knowledge regarding the rheumatic diseases by arranging Congresses, by the publication of a Yearbook (Second Edition, 1955) listing the members of the constituent national societies, by contributing to scientific publications, and by assisting personal contact and coöperation between research workers of different countries.⁵⁸⁶ The Eighth International Congress of the League was held in Geneva and Aix-les-Bains in 1953; and the Ninth International Congress is being organized by the Canadian Committee and will be held in Toronto, Canada, June 23 to 28, 1957. Congresses were sponsored in Barcelona in 1951 and in The Hague in 1955 by the European League. The first Congress sponsored by the Pan American League was held in Brazil in 1955.

In Great Britain there has been increasingly active attention to research, treatment and social welfare in the rheumatic diseases. In 1950 a committee of the Royal College of Physicians was formed to consider the organization of the treatment of chronic rheumatic diseases with special reference to the needs of the National Health Service. This committee recommended that regional centers be established in association with teaching hospitals and with a university linkage where possible. Such centers have now been established at Sheffield, West London Hospital, London Hospital, Bath, Edinburgh, Manchester and Taplow, and are primarily concerned with research, teaching and treatment. The Nuffield Foundation has extended its support of fundamental research by grants of £70,000 to the University of Manchester, and of £27,000 for new facilities at the University of Edinburgh. The British Empire Rheumatism Council, founded in 1936, has contributed immeasurably to furthering

research and education in this field.

Another sign of the growing importance of rheumatology is that in recent years professorships have been established in many universities. In 1952 a chair of Rheumatology was established in Belgium, and permanent Departments in Rheumatology were founded in two universities in Denmark—Copenhagen and Aarhus. The first British chair in Rheumatology was established at the University of Manchester in 1953. At the Postgraduate School of Medicine of the University of Brazil, a professorship in Rheumatology was founded in 1954. Professors serve as chiefs of departments of rheumatic diseases in the following European cities: Paris, Louvain, Naples, Lund, Budapest, Stockholm, London, Manchester, Edinburgh, Leeds and Bristol.

In the United States the announcement by Doctors Hench, Kendall, Slocumb, and Polley in 1949 of the dramatic effect of cortisone and ACTH in a variety of rheumatic diseases accelerated research activities to a degree still difficult to comprehend. With these scientific developments the fight against rheumatism has moved rapidly forward on many fronts. The American Rheumatism Association increased its membership to more than 1,100 physicians in 1955. This represents a phenomenal increase in the preceding five-year period. To keep pace with the rapid scientific developments, interim scientific

sessions were held in 1954 and 1955 at the Clinical Center of the National Institutes of Health, Bethesda, Maryland.

One result of this new interest has been the establishment and development of the National Institute of Arthritis and Metabolic Diseases as a constituent institute of the principal research arm of the United States Public Health Service. Authorized by Congressional action in 1950 within the framework of the Federal Department of Health, Education, and Welfare, this institute has grown within a few years to discharge its responsibilities with respect to research and training. Under its first Director, Dr. Russell M. Wilder, the extramural program of support was broadened and a branch for clinical investigation was developed at the Clinical Center in Bethesda. Since February, 1951, the extramural program has provided support for research and for training of both investigators and clinicians in the field of rheumatic diseases at universities, medical schools, hospitals and clinics. In its first 18 months of operation, this program provided research funds of over \$500,000 for 45 research projects dealing with arthritis. Both the interest in and need for research and training are reflected by the increase in public funds allotted to this institute each year; the total budget for 1954 exceeded \$7,000,000. The need for improved facilities for training of physicians in the clinical aspects of the rheumatic diseases has been recognized by the recent development of a program of training grants. In the laboratories of the Institute and in the Clinical Center a broad program of fundamental and clinical investigation is contributing to understanding and effective treatment of rheumatoid arthritis, gout and other rheumatic diseases.-Ed.] The organization and principles of operation of this institute were described by Wilder. 2246

In the United States, the Arthritis and Rheumatism Foundation has moved rapidly towards the goals for which it was established in 1948. In the 39 chapters in 34 states, and under the leadership of Mr. Floyd B. Odlum as Chairman, and General George C. Kenney as President, a nation-wide appeal for funds raised \$1,478,953 during the fiscal year 1953-1954. A major portion of the funds available on a national scale has been allocated for research in the fundamental sciences. A fellowship program, inaugurated in 1951, has encouraged many promising young scientists to enter the field of arthritis research. In addition to this national basic research program, the chapters have contributed to the support of clinical research, and the graduate and undergraduate training of doctors, nurses and physical therapists in the diagnosis and care of arthritis patients. This Foundation has expanded medical knowledge about the rheumatic diseases by distributing to physicians and medical students the following scientific publications: Primer on Rheumatic Diseases, Tenth Rheumatism Review, Bulletin on Rheumatic Diseases, Home Care in Rheumatoid Arthritis, and The Manual for Arthritis Clinics. 1142 At the chapter level, the funds from this Foundation have improved the care of arthritis patients in clinic, hospital, and in the home. In home-care programs for arthritic patients unable to attend clinics, nurses and physiotherapists have been employed to teach the patient and the family simple home methods of physical therapy. The comprehensive public education program of the Foundation has effectively extended the knowledge of the social and economic costs of the rheumatic diseases, and of the work being done in research to improve care, and in rehabilitation. 1118, 1290

The Canadian Arthritis and Rheumatism Society has carried out similar activities with respect to improving facilities for treatment of patients with arthritis and to establishing effective educational programs. In 1955 this Society received over \$800,000 in voluntary contributions. Among its unique activities has been the pioneering of the development of mobile physiotherapy units.

Worldwide attention is being focused on the role of physical medical measures in the restoration of the disabled arthritic to the activities of daily living. 428, 478, 1154, 1817, 1992 The attitude of the public toward rehabilitation is being changed from one of fear and aversion to one of hope by a program of education sponsored by such groups as the United Nations, the World Veterans Federation in Paris, and the International Society for the Welfare of Cripples; and in the United States by the President's Committee for The Employment of the Physically Handicapped. The Institute of Physical Medicine and Rehabilitation at the New York University–Bellevue Medical Center has demonstrated the indispensable role of the integrated efforts of medical, surgical and physical therapy, and of occupational therapy, psychotherapy and vocational training in the rehabilitation of the disabled arthritic patient. Other centers for comprehensive rehabilitation are now operating in Boston, Chicago, Kansas City, Santa Monica and Vallejo.

Not the least of the forces behind the worldwide movement against this greatest crippler of mankind is the arthritis patient himself. Outstanding leaders in the American Arthritis and Rheumatism Foundation and in the Canadian Arthritis and Rheumatism Society have firsthand knowledge of the disabling power of these diseases. It was emphasized that all official and voluntary organizations approaching arthritis as a public health problem have the common ultimate objective—to help the physician provide treatment of maximal effectiveness for his patients.²²⁴⁶ "A problem older than history has suddenly encountered the rise of a national voluntary agency, the advent of more effective therapy, and the establishment of a Federal program of arthritis research. We have entered a new era of medical study and practice in this field" (Wilder ²²⁴⁶).

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CASE REPORTS

COMA AFTER MILTOWN OVERDOSE *

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THE anxiety states are so common that new sedative drugs are constantly being sought. Recently, the propanediol derivatives seemed to be among the most promising. The newest compound of this type is meprobamate (Miltown) (2-methyl-2-N-propyl-1,3-propanediol dicarbamate). The chemical was first synthesized in 1950 by Ludwig and Piech.1 The pharmacology was first described by Berger.2,3 He demonstrated that it produces muscle relaxation and sedation through its action on the central nervous system by its inhibiting effect on the internuncial circuits. It is considered a practical, safe and clinically useful central nervous system depressant.

Borrus treated 67 patients with no ill effects. Selling,5 in treating 187 patients, reported three cases of allergic reaction (fever, urticaria, fainting spell), five of gastric discomfort, and one of marked sleepiness after ingestion of 20 gm. over a period of one hour. He concluded that the drug may be considered comparatively non toxic.

We wish to report a case of coma following the ingestion of 10 gm. of Miltown.

CASE REPORT

A 50 year old white female was admitted to the medical wards of Cumberland Hospital at 5 p.m. on January 12, 1956. She had been found unconscious in her room one hour previously. No friends or relatives were with the patient and so no history of the illness was immediately available. Physical examination revealed the following: Patient was in deep coma. Respirations were shallow, but 22 per minute. Lips were slightly cyanotic. Pupils were constricted and did not react to light. Corneal reflexes were absent. Patient was in complete areflexia. Blood pressure was 90/70 mm. of Hg; heart rate was 98/min.

A tentative clinical diagnosis of barbiturate poisoning was made and the patient was placed in an oxygen tent and given caffeine sodium benzoate, gr. 71/2 intramuscularly, procaine penicillin intramuscularly, 1,000 c.c. normal saline intravenously, and picrotoxin. Picrotoxin, 2 c.c. (6 mg.), was given intravenously, followed by 2 c.c. (6 mg.) intramuscularly every 30 minutes. Patient was observed closely. Fifteen minutes after the administration of the intravenous picrotoxin the corneal reflexes reappeared and the blood pressure rose to 110/80 mm. of Hg. Thirty minutes after the intravenous picrotoxin and immediately prior to the first intramuscular injection the pupils reacted sluggishly to light, although the deep tendon reflexes were still absent. Thirty minutes later the patient had sluggish knee

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jerks. After the fourth dose of picrotoxin (total of 8 c.c., or 12 mg.), the patient showed complete return of normal reflexes and made a complete recovery.

History obtained from the patient revealed that she had taken 25 tablets of Miltown (total of 10 gm.) in a suicidal attempt on the morning of her illness. The medication had been prescribed in doses of one tablet (400 mg.) three times a day by her psychiatrist. He had treated her for involution psychosis, depressed type. She had received electric shock treatment one and one-half years before and had been on Miltown therapy for the past month. There was no allergic history, and no history of organic disease.

It may be concluded that the state of coma was induced by the ingestion of 10 gm. of Miltown. Communication with Dr. F. M. Berger reveals four cases, to his knowledge, of suicidal attempts with the drug: the first took 20 gm. within 24 hours, the result being marked sleepiness; the second ingested about 40 gm., with no serious adverse effects; the third swallowed 10 gm. in an unsuccessful suicidal attempt (details of clinical course not available); the fourth, who ingested 9.6 gm., was semisomnolent but arousable.

Miltown, a comparatively safe tranquilizing agent, rarely produces toxic reactions. However, in a susceptible individual the drug in moderately large doses may produce unconsciousness to the degree of coma. Picrotoxin, an analeptic, is a safe, efficient antidote. It is recommended that when Miltown is used in increasing doses the patient remain under observation by the physician, since only frequent examinations will enable him to detect a toxic effect of the drug.

SUMMARY

A case of coma following the ingestion of 10 gm. of Miltown is reported. The patient recovered following the use of picrotoxin, oxygen and fluids intravenously.

ACKNOWLEDGMENT

The authors wish to express their thanks to Dr. S. P. Bailey for his cooperation.

SUMMARIO IN INTERLINGUA

Es reportate un caso de coma post ingestion de 10 g de Miltown (meprobamato). Iste droga es un derivato de propanediol e effectua relaxation muscular e sedation in consequentia de su action inhibitori super le circuitos internuncial in le systema nervose central.

In un serie de casos previemente reportate, 67 patientes ingereva le droga sin effectos adverse. Un altere reporto de un serie de 187 patientes mentiona solmente tres casos de reactiones allergic (febre, urticaria, lipothymia), cinque casos de disconforto gastric, e un caso de marcate somnolentia post le ingestion de 20 g de Miltown in le curso de un periodo de un hora.

Un feminina blanc de 50 annos de etate esseva admittite al hospital in coma e complete areflexia. Le tractamento consisteva de picrotoxina, oxygeno, e fluidos intravenose. Le patiente se restabliva completemente. Le historia del caso revelava que le patiente habeva ingerite le matino del mesme die 25 tablettas de Miltown (un total de 10 g) in un tentativa de suicidar se. Illa habeva essite sub tractamento psychiatric pro psychosis involutional del typo depressive.

Miltown es un agente tranquillisante de comparativemente alte securitate e produce reactiones toxic in rar occasiones. In individuos susceptibile le droga in moderatemente grande doses pote producer inconscientia del grado de coma. Es

recommendabile que patientes qui recipe Miltown in dosages crescente remane sub observation medical, proque solmente frequente examines rende possibile le detection de effectos toxic del droga.

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THE SYNDROME OF INTESTINAL CARCINOID, PULMONARY VALVULAR STENOSIS AND CUTANEOUS FLUSH *

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THE details of the comparatively new and, indeed, bizarre clinical entity of argentaffinoma, pulmonary stenosis and cutaneous flush are not well documented. Patients with this triad present a confusing picture, since the findings appear at present to be completely unrelated. Until recently the problems in diagnosis have, with few exceptions, continued to necropsy. Some evidence has been accumulated which suggests very strongly that the intestinal disease and cutaneous signs are related. The heart disease is not always overt and, when found to be a pulmonary stenosis, serves to link the three parts of this triad into a well defined disease. In some of the reports the manifestations of the heart disease were the presenting symptoms; in others, such as the one that we shall relate, it remained practically unsuspected. The disease thus serves as a link in medicine, of interest to the cardiologist as well as to the gastroenterologist.

The present report is that of a prolonged illness with the classically inexorable course of a malignant disease; the findings at autopsy were those of pulmonary and tricuspid valvular endocarditis with pulmonary valvular stenosis, in addition to widespread metastases from a primary carcinoid of the ileum.

CASE REPORT

This patient was observed for the first time on November 5, 1949, at the age of 52, because of a perinephric abscess. He was treated conservatively and improved

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gradually. A history was elicited of periodic diarrhea and cramping abdominal pain dating back to 1938. He had been to several physicians but, because of no improvement, had sought aid elsewhere, and in 1940 was seen at a large clinic. There an examination revealed "masses in the hypogastrium," and bilateral nephrolithiasis on excretory urography. Renal function was good. He was explored surgically and numerous carcinoids were found which apparently arose from the terminal ileum and which had invaded the mesentery and liver. Because the lesions were obstructive in nature, a resection with ileoileostomy was done. A gain in weight and relief of symptoms ensued. Previous surger, had included a hemorrhoidectomy in 1942, a right inguinal herniorrhaphy in 1946, and in 1949 excision of some small, "suspicious" lesions from the lower lip, which proved to be inflammatory. He was last seen at that clinic in 1949, and it was noted then that the liver edge, which had been palpable and apparently increasing in size, was palpable 8 to 10 cm. below the costal margin, and that the edge of the spleen was just felt. The blood pressure was 130/80 mm. Hg. Except for pyuria, other laboratory findings, the chest roentgenogram and blood count remained normal. Bromsulphalein retention (grade 1) was noted.

During October, 1949, there was recurrence of abdominal pain and diarrhea. The pain was described as diffuse in the lower abdomen, cramping, recurrent, unrelated to meals, and relieved to some degree by defecation of a foul-smelling, watery brown stool, together with much flatus. He was given Sorlate and multivitamins by his physician, but obtained little relief except that the character of the feces changed so that they were now mushy and slightly foamy. It was shortly afterward

that he was seen because of a perinephric abscess.

The positive physical findings were: pallor, emaciation, bilateral exophthalmos, a nodular hepatomegaly to the level of the iliac crest, a palpable spleen, and a remarkably stenosed anorectal ring. During examination the patient developed a peculiar, blotchy erythema about the face and neck. Blood pressure was 130/80 mm. Hg. Fluoroscopy of the chest revealed the cardiac chambers and great vessels to be normal in contour and size. The hilar markings were exaggerated. In contrast to the left diaphragm, the right diaphragm was elevated and limited in motion. The patient was given parenteral and oral multivitamins, powdered opium when needed, Sorlate and, because of its anabolic effects, a course totaling 250 mg. of testosterone,

which was attended by a weight gain of 10 pounds.

During 1950 recurrences of watery diarrhea and abdominal pain became very severe and, in November of that year, almost uncontrollable. In December he developed edema of the legs. It was not very responsive to mercurials and sodium restriction. At that time a soft systolic murmur maximal in the left fourth interspace was heard for the first time. He was found to have a moderately severe normocytic anemia and was given whole blood. This was of definite value, in that strength returned and the edema of the legs disappeared. A liver profile at that time showed little evidence of measurable hepatic insufficiency. X-ray studies demonstrated a remarkably rapid transit rate of barium through the small intestine-only 45 minutes were required for a column of barium to reach the midtransverse colon. In March, 1951, the patient experienced severe painful tetany, which responded to calcium gluconate, vitamin D concentrate, and increased oral intake of calcium. In July, 1951, he described for the first time a state characterized by rapid heart action, perspiration and a hot, blotchy flush. Each of these lasted about 10 minutes and then subsided. This occurred most frequently during or after meals but was also present on other occasions, such as at times of excitement and other provocative situations. When he was seen during one such episode the cutaneous changes were similar to those present at the first examination. The spontaneous flushing had been noted many times since the first visit. It was noted then, too, that the liver was more nodular. The diarrhea was aggravated by increasing dietary fat.

During the last few months of 1951 a series of abscesses appeared over the back, chest and abdomen from which diphtheroids were cultured. During the very cold winter of 1951–52 the patient was observed to be cyanotic outdoors, but of a peculiar grayish blue color. This completely disappeared with warming. Blood studies for abnormal proteins were nonrevealing. In May, 1952, hematuria was observed at the end of urination. After appropriate preliminary studies the patient was cystoscoped, and a small, sharp faceted stone was removed from the bladder. This relieved the hematuria. In August, 1952, a series of episodes of chills began, and later of right lower quadrant pain. In September, 1952, he entered the hospital for the last time, exhausted, emaciated and very weak. The final event was a rapid onset of jaundice, with evidence of progressive hepatic and renal failure, and death.

Autopsy: At autopsy there were massive metastases to the liver, mesenteric, hepatic and peripancreatic lymph nodes, with direct invasion of the pancreas. In the heart a healed endocarditis of the tricuspid and pulmonic valves was found with stenosis of the pulmonic orifice. An acute myocarditis was present. The exact description of the heart is quoted from the autopsy protocol: "The heart is of normal size, shape, and consistency. It weighs 300 gm. However, it seems that the right ventricle and the right auricle are slightly larger than usual. The right atrium is slightly to moderately dilated. The foramen ovale is closed. The tricuspid valve instead of being thin, delicate, and transparent, shows diffuse thickening along the free edge and the line of closure. In one area the free edge appears rolled. In another area a small bluish cystic structure filled with a slightly hemorrhagic material can be made out. It measures from 1.5 to 2 mm. in diameter. There are no verrucae or vegetations along this valve, either on the ventricular or on the auricular surface. The chordae tendineae are shortened, thickened and some of them are fused together. The papillary muscles are slightly flattened. The right ventricle is moderately dilated and measures 0.4 cm. at the tricuspid valve, pulmonic valve, and lateral wall. The subepicardial fat tissue is not very abundant and does not appear to infiltrate the underlying myocardium. The pulmonic valve instead of being thin, delicate, and transparent seems to have been eroded. Almost half to two-thirds of the valve is absent. The remainder of the valve is much thicker than usual, it is yellowish in color and in areas it appears rolled up. There is also evidence of subcommissural fusion. The entire valve gives the appearance of being shrunken and the pulmonic orifice subsequently appears stenotic. It admits one finger and measures only 5.5 cm. in circumference. The pulmonic artery proper shows very minimal atherosclerosis. In contradistinction to the right side, the left side of the heart shows very minimal and almost insignificant changes. The left atrium is very slightly dilated: there is also slight subendocardial fibrosis. The mitral valve shows slight atherosclerotic thickening along the line of closure. There is however no evidence of endocarditis, recent or old. The chordae tendineae are slightly thickened but neither shortened nor fused. The papillary muscles are flattened. The aortic valve is thin, delicate, and transparent, except for slight atherosclerotic thickening at the base of the cusps. The coronary ostia are not narrowed. The aorta and the coronary arteries show very minimal arteriosclerosis and atheromatosis."

Microscopically there were moderate cloudy swelling and disjunction of the muscle fibers. The interstitial tissue was fibrotic and edematous. This was true mainly in the perivascular spaces. It contained, in addition, a good number of histiocytes, and some fibroblasts, granulocytes and red blood corpuscles. The endocardium was somewhat thickened. The epicardium was thin. The intracardiac arteries and arterioles showed minimal intimal thickening. Several sections of the heart valves showed marked thickening, hyalinization and vascularization of the valves. In addition, calcific foci were seen.

DISCUSSION

The earliest descriptions of this syndrome were made independently by Cassidy 1 and by Scholte. Cassidy's patient was reported as a case of abdominal carcinomatosis with probable adrenal involvement. His patient had flushing of the face, recurrent diarrhea, palpitation, dyspnea, and an epigastric tumor associated with a large mass in the pelvis which was also palpated rectally. There was a loud, blowing systolic murmur, heard best in the fourth intercostal space. Dilated venules were present over the nose and cheeks. As in our patient, the phenomenal flushing was exaggerated during emotion, and either during or shortly after meals. Cassidy's patient came to necropsy and, in another report, he indicated that, in addition to regional and distant metastases, the heart showed a "well marked stenosis of the pulmonary valve." The original tumor was thought to be a carcinoma of the prostate.

Scholte's patient was known to have had telangiectases about the face since youth, and developed diarrhea and symptoms referable to the heart years before death. His patient had an enlarged heart with abnormal murmurs, and died in congestive heart failure. At necropsy there were carcinoid tumors of the small intestine with extensive metastases, and a chronic endocarditis of the tricuspid and pulmonic valves with pulmonic stenosis and endocardial thickening in the right atrium. The skin lesions were said to be telangiectatic angioma.

The first reference to this disease in the American literature is that of Björck, Axen and Thorson in 1952.4 Their patient was also a male who had a reddish blue cyanosis over the body, most marked on the face and trunk. In addition, there were dyspnea at rest, ankle edema, and a brownish, scaly thickening of the skin on the extensor surface of the forearms. Under stress the cyanosis was noted to have changed evanescently into a vermilion color, particularly over the chest and abdomen. Postmortem examination revealed a tumor in the middle of the small intestine with a marked hepatomegaly in which the liver was filled with large yellow metastases. There was stenosis of the pulmonary valve, but no signs of endocarditis. The tricuspid valve was thickened. Björck et al. also observed a patient with the intestinal and cardiac findings but without flush. They related briefly an observation of Waldenström, who had seen a patient with intestinal carcinoid and vasomotor symptoms but with no heart disease.

In 1953 Rosenbaum et al.⁵ reported two cases with profound telangiectases about the face, abdomen and upper extremities, who developed congestive heart failure and at autopsy had pulmonary and tricuspid valvular stenosis. One had a carcinoid of the ileum and the other had an adenocarcinoma of the bile ducts. Both had extensive hepatic metastases.

Isler and Hedinger ⁶ reported three cases; in each there were cyanosis and cardiac murmur, and at autopsy carcinoid tumors of the small intestine with hepatic metastases, pulmonary stenosis and tricuspid valvular endocarditis. Ljung's ⁷ report in 1953 dealt with a male who had an intense red discoloration of the face which at first occurred only periodically but toward the end of his life was almost constant. He found carcinoid tumors in the intestine with hepatic metastases. Hedinger and Gloor ⁸ were more specific in their report in 1954, and precisely defined a triad of abdomial, cardiovascular and cutaneous

findings. In their most recent report Thorson, Björck, Bjorkman and Waldenström ⁹ described two more definite cases and discussed others, some of which had been proved.

It is notable that in the few cases reported there appear to be certain discrepancies regarding the presence or absence of cyanosis, telangiectases, and distribution of red discoloration. Any combination of these signs may be seen. Variations in gastrointestinal symptoms and signs are noted, and extend from a totally unsuspected or minimal disease to a clinically dominant complex.

Our patient's intestinal complaints and findings almost completely dominated the syndrome and formed the most significant part of the triad. He was not a cardiovascular cripple, as contrasted with the patient reported by Björck. Our patient did not present persistent cyanosis nor did the red discoloration appear on the arms and breast. Thus the entity varies as to the severity of

each part of the triad.

Carcinoid tumors occur most commonly in the appendix and frequently in the small intestine. The growth consists of masses of spheroidal cells with a vacuolated or granular cytoplasm. The cells are rich in lipoid material, which gives the tumor a yellow coloration. The tumor is considered to be an endocrine system tumor arising from Kultschitsky's cells of the chromaffin system of the intestinal mucosa. These cells stain intensely by silver impregnation, and the tumor is thus termed an argentaffinoma. Carcinoid tumors of the small intestine are frequently multiple and may produce obstruction. Of the approximately 25% which metastasize, the spread is to regional lymph nodes and liver. This tendency is seen uncommonly in carcinoid of the appendix. It is therefore understandable that the intestinal symptoms have varied in the few reports of the syndrome. However, the flushing, which is discussed later, does not seem to vary directly with the extent of the carcinoid. It occurs only if the carcinoid is present. There is no quantitative relationship.

Periodic blotchy flushing of the skin was a consistent sign. The distribution varied in certain respects, in that our patient neither displayed flushing nor reported having had it on any part of the body other than the face and neck. The usual events of the flush occurred with excitement or in relation to meals, either at the end of a meal or shortly after it was completed. A sensation of warmth was quickly followed by areas of redness, frequently starting on the neck and extending to the face and forehead. The reddened areas quickly defined themselves as blotchy, elevated, almost urticarial appearing lesions of irregular shape. There was no evidence of pallor in the elevations, and no pruritus. The areas of redness were warmer than the surrounding nonflushed skin. Beads of perspiration could be seen about the face. At times the flush coalesced. After a short period of time it could be seen to disappear, leaving no residue. Blotchy flushing is occasionally seen in young individuals, especially "teen age" females, who exhibit this change—which is in sharp contrast to the so-called blush-during physical examination. The flush is to be differentiated from that seen in anger. Here it is diffuse and definitely not blotchy. The alcoholic flush is also diffuse but of longer duration. The flush has been a consistent sign in patients reported previously. Waldenström is quoted as having categorically stated that the presence of the flush was an absolute indication of the presence of carcinoid tumors.6

Perhaps the earliest indication of a mechanism for the production of the flush, etc., relates itself to the classic experiments of Vialli and Erspamer. They were able to isolate a substance from the rabbit gastric mucosa and spleen and provisionally identify it as a polyphenolic amine. It was later shown to be a 5-hydroxy indole base combined with equimolar parts of creatinine and sulfuric acid. The Because of its origin from the enterochromaffin (argentophile) cells of the gastrointestinal tract, Erspamer called it "enteramine." It may be extracted from normal intestinal mucosa but is recovered in increased quantity from carcinoma tissue and in maximal amounts from argentaffinoma. Enteramine is then a specific secretion of the enterochromaffin cells of the gastrointestinal tract. Serotonin has been shown to be circulating enteramine, and has been isolated in a pure state by Rapport, Green and Page. Lucy Subsequently this substance was conclusively identified as 5-hydroxy tryptamine by Rapport, and synthesized as such by Hamlin and Fischer.

It has been demonstrated that protein extracts of lung can actively destroy serotonin.¹⁴ Blaschko suggested that enzymatic degradation of 5-hydroxy tryptamine may be due to amine oxidase. More recently, Gaddum indicated that some substances which, like 5-hydroxy tryptamine, contain an indole nucleus, compete with 5-hydroxy tryptamine for the same tissue receptors and prevent its action.¹⁵ Apparently the most potent of these is lysergic acid diethylamide, which has a remarkably antagonistic action to 5-hydroxy tryptamine. It is further known that 5-hydroxy tryptamine is converted by liver and excreted

in the urine as 5-hydroxy indole-acetic acid.

Erspamer 16 found the serotonin content of serum to be inconstant, conforming to a pattern of greater concentration in younger persons. Reid and Rand 17 showed that a rise in both the pulmonary arterial and the systemic arterial pressures could be elicited by intravenous injection of incompletely purified serotonin. They also elicited a rise in pulmonary arterial and right ventricular pressure on injection of 5-hydroxy tryptamine. This rise was produced in cats by either intravenous or right atrial injection, and the effect was not abolished by vagotomy. Comroe 18 obtained similar results. Injection of 5-hydroxy tryptamine into the left ventricle did not cause a rise in right ventricular pressure, although bradycardia and apnea occurred; nor was there a decrease in filling or output in the left ventricle. Page and McCubbin 19 suggested that serotonin may be a naturally occurring vasodilator compound with a remarkable ability to regulate peripheral neurogenic vasomotor tone. Reid and Rand 20 injected 5-hydroxy tryptamine intradermally and obtained a red, often morbilliform reaction without itching or whealing at the site of the injection. 5-hydroxy tryptamine has a pronounced effect on intestinal motility. In animals subjected to deep anesthesia, exhibition of this substance may cause evacuation of the bowels and noticeably increased peristaltic activity. This substance therefore acts as a whip to the intestine, not only by increasing peristalsis, but also by liberating additional amounts of a substance which causes a periodic flush and which is then a manifestation of vasodilation. Since vagotomy and the use of vagolytic drugs do not affect either the peristalsis or the flush, the inability of the lung to destroy this material may have importance. It is suggested, then, that the lung is unable to handle the excessive amounts of 5-hydroxy tryptamine. Attention must be given to the frequent occurrence of

flushing as related to meals. In our patient it was thought to represent, among other signs and symptoms, a feature of the dumping syndrome. Whether this means primary vagal stimulation or liberation of 5-hydroxy tryptamine from the jejunal mucosa is uncertain. Nevertheless, it is significant because our patient was definitely able to relate such occurrence to meals as well as to emotional upheaval.

When flushing occurred in relation to meals, there were invariably associated weakness, perspiration and tachycardia. The intermittency of skin changes may be explained by the sudden increased liberation of enteramine from the

tumor and fading by detoxification.

Liberation of 5-hydroxy tryptamine is probably a continuous process, with additional amounts being occasionally put into the circulation in quantities that

are apparently beyond the threshold for handling this substance.

The presence of pulmonary and tricuspid valvular endocarditis with pulmonary valvular stenosis was completely unsuspected in the absence of neck and liver signs, cyanosis, significant murmurs, thrill and abnormal fluoroscopic findings. Pulmonary stenosis with closed septa is cyanotic, but the cyanosis appears only with right heart failure. This patient had never been in failure and therefore cyanosis was not noted. In other reports reddish blue cyanosis was a striking feature of the disease. Though peripheral edema was seen in our patient, the episodes of edema were rapidly cleared after infusion of whole blood and plasma. It will be recalled that cyanosis was present late and only in cold temperatures, and disappeared with warming. It was therefore peripheral cyanosis. No murmurs were heard for at least a year after our observations began, and then they gradually increased in intensity so that at the end of life the systolic murmur was moderately loud. No thrills were palpated. The changes in the pulmonary valve were unlike those seen in congenital pulmonary valvular stenosis, either as a part of another congenital cardiopathy or as an isolated disease, though isolated pulmonary stenosis without associated ventricular septal defect is not rare. Rheumatic fever may affect the pulmonary valve in the acute phase of the disease, but it rarely leaves any deformity. There is no evidence for either acute or subacute bacterial endocarditis. Thus it appears that the valvular changes are bizarre and acquired. The patient reported by Björck et al.4 was the youngest of any reported in the available literature. His patient had symptoms for many years which may have antedated the intestinal lesion. It is well established that carcinoid does not ordinarily lead to a rapid demise. More characteristically, there is a slow course. At first there may be no clues to the presence of the tumor, for only when symptoms appear are they investigated and a diagnosis made. A congenital valvular lesion would probably have manifested itself long before. Though unlikely, an acquired lesion due to another cause may have produced symptoms earlier and actually have been reported in such a time sequence. The murmur takes time to develop and in our patient it occurred late. It was heard loudest in the fourth intercostal space, and was unaccompanied by a thrill. Signs suggestive of tricuspid disease were not elicited. Fluoroscopic examination did not reveal chamber changes or pulmonary vascular alterations. One would expect to see these if the pulmonary stenosis was complication by heart failure.

For our purposes the selective activity of 5-hydroxy tryptamine for measur-

able alterations in dynamics concerns itself chiefly with the right heart. Because the valve changes are of such a remarkably different character than those seen in congenital pulmonary valvular disease, rheumatic fever or bacterial endocarditis, it appears that they are secondary to an unusual action of 5-hydroxy tryptamine.

It is suggested that a specific tissue response of vascular endothelium, particularly in the chambers of the right heart, plus alterations in pressure due to 5-hydroxy tryptamine, are probably involved in the pathogenesis of the valvular disease after the intestinal lesion is well developed.

We have thus been confronted by a serious though uncommon disease with numerous facets. While admittedly the carcinoids may remain unsuspected until prominent gastrointestinal symptoms occur, it is within the realm of clinical suspicion to look for such lesions when there is an associated characteristic flush. The patient may not present overt evidence of pulmonary or tricuspid valvular disease. On the other hand, in those instances in which the dominant feature of the triad is the heart disease, evidence of blotchy flushing with or without intestinal complaints may be the earliest clue.

The disease is thus a well defined triad of argentaffinoma, pulmonary and tricuspid valvular endocarditis with pulmonary stenosis, and a characteristic blotchy flush. It is felt that the carcinoid precedes the appearance of the other features of the disease.

Conclusions

- 1. A triad exists of intestinal carcinoid, pulmonary and tricuspid valvular endocarditis with pulmonary stenosis, and a blotchy flush.
 - 2. The presenting symptoms may be either intestinal or cardiovascular.
- 3. A characteristic blotchy flushing is the most easily recognized feature of this disease.
- 4. The liberation of 5-hydroxy tryptamine from the tumor is suggested as the etiologic agent for the endocarditis and flush.

SUMMARIO IN INTERLINGUA

Es presentate un caso in que le principal constatationes clinic esseva carcinoide, rubescentia cutanee, e stenosis pulmono-valvular. Tumores carcinoide se origina in le cellulas de Kultschitzky del systema chromaffin del mucosa intestinal. Illos es frequentemente appellate argentaffinoma a causa de lor intense coloration per le impregnation de argento. In tal casos, accessos de rubescentia del facie e del collo occurre le plus frequentemente al tempore del repastos e sub excitation emotional. Iste rubescentia pote durar variabile periodos de tempore e dispare spontaneemente.

Morbo pulmono-valvular pote esser non-suspicite in le absentia de associate symptomas cardiovascular. Cyanosis es usualmente un characteristica frappante del morbo. Le alterationes valvular in le presente patiente differeva ab illos observate in omne altere morbo valvular.

Es cognoscite que le tumor emana 5-hydroxy-tryptamina, que es identic con serotonina. Hyperserotoninemia produce un augmento del pressiones pulmono-arterial e dextero-ventricular, acceleration del activitate peristaltic intestinal, e accessos de rubescentia. Es exprimite le opinion que un specific historesponsa del endothelio vascular, specialmente in le cameras del corde dextere, insimul con alterationes del pression effectuate per serotonina, es implicate in le pathogenese del lesiones cardiac de iste syndrome.

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HODGKIN'S SARCOMA SIMULATING VENTRICULAR ANEURYSM *

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According to a number of reported autopsy series, infiltration of the myocardium by nests of malignant cells is not rare in Hodgkin's sarcoma, nor are small nodules on the pericardium.1 However, large tumor nodules involving the heart are uncommon. Rottino and Hoffmann 2 reviewed the world literature in 1952 and were able to find only five cases of tumor involvement of the heart in Hodgkin's disease, and they reported a sixth case. All of these cases showed a tumor mass in the right auricle, usually occluding the orifice of the inferior vena cava.

The present case appears to be unique in that the massive tumor involved



Fig. 1. Chest roentgenogram showing the similarity of the tumor to a ventricular aneurysm.

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all chambers except the right auricle, and showed roentgenographic findings suggesting ventricular aneurysm.

CASE REPORT

A 63 year old white male auto mechanic was admitted to the Oklahoma City Veterans Administration Hospital on February 7, 1955, complaining of pain in the right upper quadrant of the abdomen for two months. Three years previously he had had an abdominal operation at another hospital for "cancer of the stomach"; apparently a portion of the stomach and the gall-bladder had been removed. Review of the tissue slides from that hospital, however, revealed only chronic inflammatory changes. Eighteen months before admission he developed postprandial vomiting. Two months before admission he became jaundiced and developed constant, severe pain in the right upper quadrant of the abdomen which radiated to the mid-back.

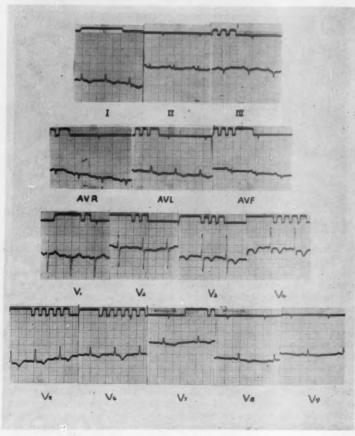


Fig. 2. Electrocardiogram, including posterior chest leads. Note the diffuse, primary T-wave changes without any QRS or ST abnormalities.



Fig. 3. The size and appearance of the tumor of the heart are shown in this photograph.

The pericardium has been opened.

Pedal edema also appeared at that time. He was seen by a physician who stated that the patient had an enlarged heart. He became progressively more ill, with anorexia, weight loss and a cloudy sensorium.

Physical examination revealed a poorly nourished, jaundiced white male with evidence of weight loss and a cloudy sensorium. Vital signs were not remarkable. The skin, sclerae and mucous membranes were deeply jaundiced. Pitting edema of the lower legs and feet was noted. The lungs were clear. The heart appeared enlarged, the left border measuring 12 cm. to the left of the midsternal line in the fifth intercostal space. No heart murmurs were heard. No unusual pulsations were observed. A healed transverse scar was present in the upper abdomen. The liver was palpated 6 cm. below the right costal margin and was tender.

Laboratory data revealed an initial hemoglobin of 9.9 gm. per 100 ml., with a hematocrit of 32%. The sedimentation rate was 30 mm./hour. White blood count was 5,700 cells/cu. mm., of which 83% were polymorphonuclear leukocytes and 17% lymphocytes. VDRL was negative. Blood nonprotein nitrogen was 35 mg.%.



Fig. 4. Cross section of the heart showing involvement of the ventricles, particularly the left.

Liver function studies revealed an alkaline phosphatase of 31 Bodansky units, a van den Bergh of 6.2 mg.%, of which 4 mg.% was direct, and a thymol turbidity of 1.5 units. Urinalysis revealed a 1 plus albuminuria, and the urine was positive for bilirubin.

X-ray examination of the chest, including fluoroscopy, showed a marked convexity in the posterior wall of the left ventricle (figure 1) suggesting a ventricular aneurysm. Radiographs of the abdomen revealed evidence of ascites. Skeletal survey failed to reveal evidences of metastases. Barium study of the gastrointestinal tract disclosed only a subtotal gastric resection.

An electrocardiogram revealed generalized, nonspecific T-wave inversions (figure 2).

On admission it was felt that the patient had obstructive jaundice, and he was scheduled for laparotomy. However, when the ventricular aneurysm was suspected, the operation was canceled and a medical consultation was requested. The medical consultant suggested the diagnosis of tumor involvement of the myocardium ante mortem because of the negative cardiac history and absence of QRS and ST segment changes on the electrocardiogram. The patient died suddenly on the fourteenth hospital day.

Autopsy Findings: When the pericardium was opened a large tumor mass was seen overlying the left ventricle, measuring 8 by 10 cm. (figure 3). The heart and tumor mass together weighed 510 gm. The mass involved the wall of the left ventricle and the right ventricle also. The left atrium was involved in the mass but not the right atrium. Most of the wall of the left ventricle was replaced by the mass; the right ventricular wall, although involved, was still recognizable as such (figure

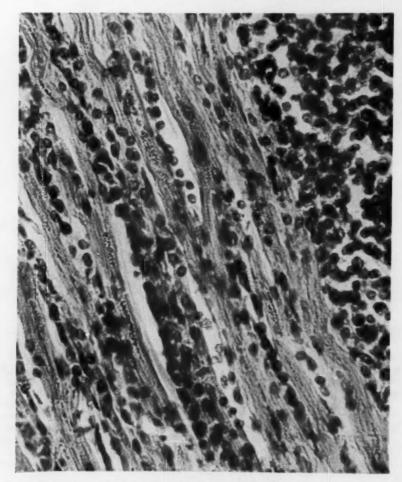


Fig. 5. Photomicrograph of a section of heart showing border of tumor and myocardium, with infiltration also of the latter.

4). When the heart was opened it was seen that the inner surface of the chambers and the valves did not appear unusual.

The liver weighed 2,950 gm.; no tumor involvement of this organ was noted. The wall of the gall-bladder was involved by tumor. The pancreas was markedly involved, and the extrahepatic bile ducts were surrounded by tumor mass. In addition, there was minor involvement of right kidney and the spleen.

Microscopic examination revealed the heart muscle to be diffusely infiltrated with small tumor cells having dark, round nuclei (figure 5). These tumor cells were also seen in the splenic capsule and, in addition, giant cells of the Reed-Sternberg type, compatible with Hodgkin's sarcoma (figure 6). This picture was also

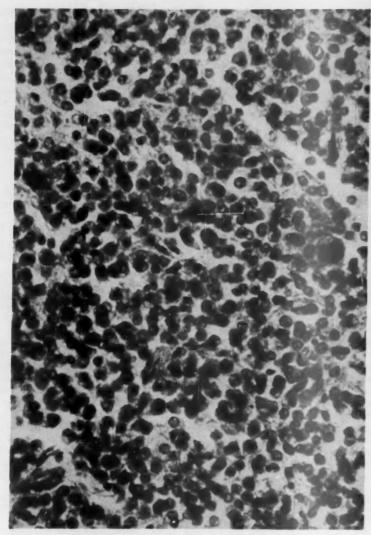


Fig. 6. Photomicrograph of a section of tumor mass demonstrating several Sternberg-Reed cells.

seen in the pancreas and kidneys, as well as in tumor nodules taken from many other areas.

DISCUSSION

This case presents several interesting features not heretofore described. Outstanding among these is the close radiologic resemblance of the cardiac

lesion to a posterior ventricular aneurysm. It is of interest in this regard that no history of previous myocardial infarction was obtained, and, although primary T-wave changes were noted on the electrocardiogram, no ST segment shifts or QRS changes were seen. It is surprising that no clinical symptoms occurred with the massive cardiac involvement. This absence of clinical symptoms with lymphomatous involvement of the heart was also noted by Nabarro ³ and by Chevallier et al.⁴ in discussing diffuse lymphomatous infiltration of the heart. Nabarro stated, however, that when such manifestations are present the most common syndrome is intractable heart failure. Low voltage and conduction disturbances on the electrocardiogram have been reported in some cases of diffuse lymphomatous infiltration; our patient showed only diffuse, nonspecific T-wave changes.

SUMMARY

1. A case has been presented of massive tumor involvement of the myocardium with Hodgkin's sarcoma simulating ventricular aneurysm roentgenographically.

 In such a case, the diagnosis of tumor involvement of the heart might be suspected antemortem by virtue of a negative cardiac history and absence of expected electrocardiographic findings of previous infarction or ventricular aneurysm.

SUMMARIO IN INTERLINGUA

Ben que le invasion del pericardio e del corde ha essite reportate in sarcoma de Hodgkin, solmente sex occurrentias de massive tumores del myocardio causate per iste morbo es a trovar in le litteratura. Es presentate un caso singular in que le massive tumor simulava sub fluoroscopia un aneurysma ventricular. Le patiente esseva un masculo blanc de 63 annos de etate. Ille esseva admittite al hospital con dolores abdominal, vomito, jalnessa, e edema. Le examine physic monstrava allargamento del corde e del hepate. Fluoroscopia del corde revelava marcate convexitate del pariete posterior del ventriculo sinistre. Isto suggereva le presentia de aneurysma ventricular. Le electrocardiogramma exhibiva solmente generalisate e non-specific inversiones de unda T.

Le necropsia revelava un grande massa tumoric que implicava le myocardio de ambe ventriculos e le atrio sinistre. Le examine microscopic monstrava que le tumor esseva un sarcoma de Hodgkin.

Le diagnose de un implication tumoric del corde esseva suspicite ante morte a causa del negative historia cardiac e del absentia del constatationes electrocardiographic a expectar in casos de previe infarcimentos o de aneurysmas ventricular.

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SYMPATHICOBLASTOMA: REPORT OF A CASE IN AN ADULT, WITH A DISCUSSION OF THE PATHOGENESIS OF CEREBRAL METASTASES *

By JOHN A. DI FIORE, M.D., New York, N. Y.

SYMPATHICOBLASTOMA is a highly malignant tumor arising from sympathetic nerve tissues; relatively rare, it is yet one of the most frequently observed abdominal tumors in children under the age of four years.1 Its occurrence in an adult is indeed a rarity, and it is for this reason that the following case is presented. In addition, the primary site finally disclosed at autopsy proved to be most interesting.

Sympathicoblastomas are known to arise most frequently from the adrenal medulla; however, they may take origin from other sympathetic tissues, such as in the paraganglionic tissue adjacent to the adrenals, in the retroperitoneal and retropleural spaces, at the root of the lungs, from the organs of Zuckerkandl near the bifurcation of the iliac arteries, and from the superior cervical ganglion.

CASE REPORT

A 52 year old male was admitted to St. Vincent's Hospital on September 5, 1951, after having had a convulsion and impairment of speech. It was later learned that for a fortnight he had been complaining of headaches and that his speech had been intermittently incoherent. On the night of admission he became rather restless, moved all the furniture about the house, had a convulsion, and was unconscious for about an hour. On examination he was conscious but dysphasic, and had evidence of right-sided weakness and a bilateral Babinski's sign. A routine chest plate was reported as negative. Lumbar puncture revealed a pressure of 162 mm. of water, and the cerebrospinal fluid showed three cells; protein was 91 mg.%. An electroencephalogram showed severe diffuse dysfunction (mixed slow type), with greater disorder of the left temporocentral region and of the right anterior temporal region. Ventriculogram and operation were performed on September 14, and in the process a large left frontal cyst containing xanthochromic fluid was entered. Adjacent to it a lot of necrotic tissue as well as neoplasm was removed which histologically looked like malignant glioblastoma.

The patient made a favorable recovery, regained his speech and was discharged to his home on September 21, 1951. He was placed on anticonvulsive medication and subsequently started to vomit. Because of the vomiting and odd behavior at home he was rehospitalized. He was confused and disoriented. There was a fluctuant mass at the site of the previous surgical incision over the forehead and bilateral papilledema. There was no Babinski's sign, and the ankle jerks were absent. On the twelfth hospital day of his second admission an x-ray of the chest showed a large, cannon-ball type lesion of the left lung (figure 1). He subsequently became euphoric, more confused and disoriented, and went rapidly downhill. He died on November 24, 1951, about 10 weeks postoperatively.

Autopsy revealed a circumscribed mass about 5 cm. in diameter in the left lower lobe of the lung extending across the fissure of the left upper lobe. The liver was involved, with a few small metastatic solid gray nodules, the largest 1 cm. in diameter.

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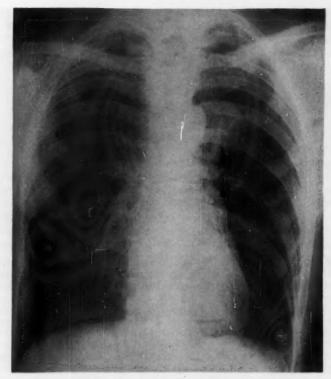


Fig. 1. "Cannon-ball" metastatic lesion in upper left lung field.

The head of the pancreas was enlarged and firm. A large tumor mass occupied the whole head of the pancreas, and many mesenteric nodes were replaced by tumor. The body of the pancreas was free of tumor. In the left adrenal gland was a small, discrete tumor 1 cm. in diameter, growing centrifugally and having the characteristics of a metastatic lesion rather than of a primary lesion. The brain showed a soft, mushy gray growth 5 cm. in diameter in the left frontal lobe extending into the parietal lobe. There were similar growths in the occipital lobe and also one in the left cerebellum.

The histology of the various tumors was identical. The cells were small, containing very little cytoplasm and mostly all nucleus, with a tendency to be arranged in whorls and grouped around blood vessels (figure 2). The histologic diagnosis was sympathicoblastoma, with its primary site of origin in the pancreas.

Discussion

In all probability this tumor started in sympathetic nerve tissue in the retroperitoneal area contiguous to the pancreas, with invasion and growth within the pancreas. This remained dormant, and the first sign of the disease was related to the cerebral metastasis.

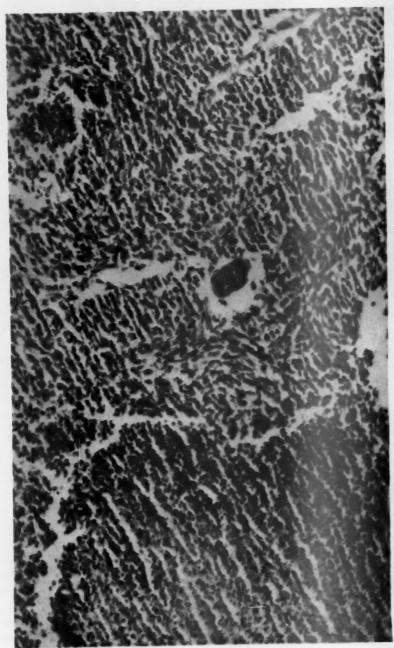


Fig. 2. Section of tumor tissue.

PATHOGENESIS OF METASTATIC TUMORS OF THE BRAIN

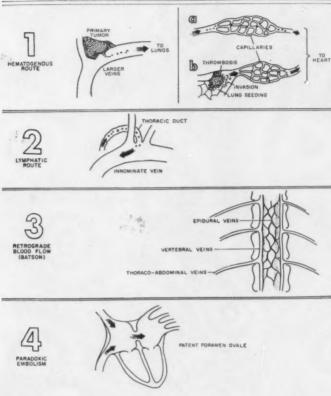


Fig. 3.

The most common pathway for metas ases to reach the cranial cavity is from the lung via the blood stream, and either primary or secondary pulmonary lesions will be found in at least 80% of cases that come to autopsy with metastatic intracranial tumor. In spite of the fact that the lung is so frequently involved, x-ray demonstration of the pulmonary lesion may be difficult or impossible. In a group of cases with verified pulmonary lesions, 35% were reported as negative from roentgenologic study.²

It is interesting to note that in a series of 30 cases a comprising metastatic brain tumors, the length of survival varied with the site of the primary tumor. Of five cases originating in the kidney, three survived beyond 24 months. Of nine cases from the breast and seven from the gastrointestinal tract, two from each survived the 24 month period. Of nine lung cases, none reached a six month survival.

Regarding the pathogenesis of metastatic brain tumors (figure 3), it has already been mentioned that the most common pathway is from the lung via the

blood stream. This will be enlarged upon shortly. There are numerous factors to suggest that the hematogenous route is the most likely one: 8 (1) the frequency of vascular involvement within the primary neoplasm; (2) the greater frequency of intracranial metastases from pulmonary cancer; (3) histologic intracranial vascular involvement by tumor cells; (4) the infarction of brain produced by tumor emboli; (5) the distribution of metastases in the brain, i.e., they occur predominantly within the gray substance or subcortical white matter, where the blood supply is most abundant; (6) the common occurrence of meta-

stases within the choroid plexus.

Assuming now that we have a primary tumor somewhere in the body, the tumor cells reach the brain through the invasion of blood vessels adjacent to the neoplasm. They penetrate the veins and produce thrombosis or endophlebitis. If smaller vessels are involved, occlusion may occur rapidly with no dissemination. If larger vessels are invaded there occurs only partial obliteration of the lumen, and hence prolific liberation of tumor emboli. These consist of isolated cells, clumps of cells or fragments of tumor thrombi composed of tumor cells clothed by fibrin, red blood cells, white blood cells and platelets. The smaller emboli or isolated cells may pass through the wide pulmonary capillaries to the left side of the heart without stopping. The larger ones will be arrested in the lungs as cancerous thrombi, where they may start growing to produce pulmonary lesions and later may break through into the pulmonary veins, to be carried to the left side of the heart and finally up to the brain.

Even when the tumor cells spread originally through the lymphatics, they eventually reach the nervous system through the blood stream by way of the

thoracic duct, right lymphatic duct or their tributaries.

A third method of pathogenesis involves retrograde blood flow in thoracoabdominal veins. This method was worked out by Batson,4 who verified his dissections with injection experiments. It has been found that with abdominal straining or coughing, or any other maneuver causing an increase in intraabdominal pressure, there is a reversal of blood flow in the thoraco-abdominal veins. These veins freely communicate with the vertebral veins, which also communicate with the epidural veins surrounding the spinal cord. Tumor cells, such as those from the gastrointestinal tract, may invade the abdominal veins and by-pass the portal and caval systems to reach the nervous system by way of these thoraco-abdominal communications with the veins of the spinal cord.

The fourth and probably most unusual method of cerebral invasion is by way of a paradoxic tumor embolism. This method by-passes the lung barrier by means of a septal defect. As a result of this shunt there is no lung seeding, and metastatic emboli are carried into the cerebral circulation via the left side

of the heart.

SUMMARY

A case of sympathicoblastoma in an adult has been presented because of its extreme rarity and because of its most unusual origin within the pancreas. The unfolding of this case disclosed the most common method of pathogenesis of metastatic cerebral malignancies, namely, the hematogenous route through the lung fields.

SUMMARIO IN INTERLINGUA

Sympathicoblastoma es un malignissime tumor de origine nervohistic que se incontra rarmente in adultos.

Le presente caso concerne un masculo de 52 annos de etate. Ille esseva presentate con symptomas de alteration mental que indicava le implication del cerebro. Post le ablation chirurgic de lo que esseva considerate como un primari neoplasma cerebral, un roentgenogramma thoracic revelava le presentia de un grande lesion in le pulmon sinistre. Isto representava un nove indicio del origine extra-cerebral del tumor. Le patiente deteriorava rapidemente. Ille manifestava symptomas mental. Finalmente, le necropsia revelava le sito primari in le capite del pancreas. Isto es un inusual- e interessantissime occurrentia.

Un revista de morbos metastatic del cerebro indica que circa 80% del casos es characterisate per le implication del pulmones con cancere primari o secundari. Tamen, roentgenogrammas revela lesiones definite in solmente circa 35% del casos.

Quanto al pathogenese de metastatic tumores cerebral, il se monstra que le via hematogene es le plus commun medio de transmission. Altere medios de transmission es invasion lymphatic, dissemination per retrograde fluxo sanguinee in venas thoracoabdominal, e finalmente le rar occurrentia de un si-appellate paradoxe embolismo tumoric per un defecto septal in le corde.

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EDITORIAL

THE IRRITATIVE EFFECT OF SMOKING ON THE RESPIRATORY MUCOUS MEMBRANES

For convenience in discussion we may distinguish between the immediate direct irritative action of tobacco smoke on the mucous membranes and its possible late carcinogenic effects. Because of the disturbing and ominous connotations of the word cancer, attention has been concentrated largely on this phase of the problem. There is increasing evidence, however, that the nonspecific irritative action may be even more important, particularly

as a cause of obstructive emphysema.

Familiarity tends to breed indifference if not contempt, and the "cigarette cough" resounding loudly among us and omnipresent in heavy smokers (of a pack and more a day) has been regarded more as a joke than a significant medical problem. This is true not only of the cougher but often also of his physician—who may likewise be a victim. As long as the cigarette cough means merely an uncomfortably "raw" red pharynx and frequent dry "hacks," it is probably not of great immediate significance although it doubtless predisposes to the current strains of respiratory "viruses." This probably may continue to be true during the first few years of one's smoking career, and decision as to smoking may rest upon whether the satisfaction obtained outweighs the attendant discomfort.

That this irritation and a beginning uneasiness of the public regarding the effects of smoking in general are becoming commercially significant is tacitly admitted by the manufacturers who have introduced filter tips with some modest success in removing part of the nicotine and tars (20 to 40%) and who are apt to claim that their own brand is a little less harmful than the product of their rivals. Nicotine is probably not important as an irritant, but the tars presumably are. Certainly important are the hot smoke and the minute particles of soot which can penetrate deep into the air ways and cause irritation even in the terminal bronchioles. There is general agreement that inhaled cigarette smoke is more irritating than pipe or cigar smoke unless exceptionally the latter is also inhaled.

Although many reports have appeared during the past few decades pointing out the association of smoking with chronic respiratory irritation and infection, until recently this phase of the smoking problem has received inadequate consideration. Only a few of the more important recent studies

can be mentioned here.

¹ A study of cigarettes, cigarette smoke and filters. 4. Regular cigarettes, king-size cigarettes and additional filter-tip cigarettes, (Chemical Laboratory, American Medical Association) J. A. M. A. 157: 1309–1311, 1955.

Myerson 2 in a study of smokers complaining of hoarseness and vocal fatigue observed in 143 cases a lesion of the vocal cords starting as a circumscribed edema with evidences of acute inflammation followed by fibrosis and thickening and finally by formation of a tumor which he described as an "edematous fibroma." The inflammatory edema subsided within 24 hours after smoking was stopped, but the fibromas persisted and excision was required. Similar lesions have been noted by subsequent observers, e.g. Waldbott.⁸ Such irritation may lead to hyperirritability and laryngeal spasm which may be a serious problem to anesthetists (e.g. Greene 4).

More important, however, is the involvement of the bronchi. Abbott et al.5 in a study of 294 cases of emphysema of all types with special reference to surgical measures of treatment emphasize that the disease "is not simply a degenerative disease of old age." They found "an almost constant history of protracted cough or so-called chronic bronchitis." The major causes of the cough in their series were tobacco smoking in 214 and suppuration in 209. All but eight of 209 known smokers consumed over a pack per day. They were "impressed by the destructive effects of tobacco in excess in these patients," in causing bronchospasm and edema of the mucosa of the bronchioles, resulting in partial and intermittent obstruction to the evacuation of air from the alveoli. "In a large number of instances patients who succeeded in stopping the smoking habit obtained complete subjective relief from cough and wheeze, and frequently wheezing was decreased or cured."

In Great Britain bronchitis has constituted a major problem, and attention was centered intensively upon this following the disastrous fog of December 1952 in London which caused 4000 deaths during a period of 14 days. Joules 6 has attributed this largely to air pollution, especially from smoke from inefficiently burned coal and liberated toxic gases including oxides of sulfur. Under ordinary circumstances other local factors are also important—inclement weather, prevalence of acute respiratory infections, various chronic pulmonary diseases. Joules stresses the deleterious effect of smoking as an additional cause of bronchitis. He observes that few who smoke over 15 cigarettes a day for 20 years escape a morning cough, but abstinence for three months usually proves the relationship. The 30,000 deaths a year attributed to bronchitis (besides 20,000 to pneumonia) and the 16.5 million days of lost working time make the problem practically important. Joules regards cigarette smoking as more dangerous than any

² Myerson, M. C.: Smoker's larynx: a clinical pathological entity, Ann. Otol., Rhin. and Laryng. 59: 541-546 (Aug.) 1950.
³ Waldbott, G. L.: Smoker's respiratory syndrome: a clinical entity, J. A. M. A. 151:

^{1398-1400, 1953.}

⁴ Greene, B. A., and Berkowitz, S.: Tobacco bronchitis: an anesthesiologic study, Ann. Int. Med. 40: 729-742, 1954.

Abbott, O. A., et al.: A new approach to pulmonary emphysema, Thorax 8: 116-132, 6 Joules, H.: A preventive approach to common diseases of the lung, Brit. M. J. 2:

^{1259-1263, 1954.}

other national habit and goes so far as to say that unless the irritant and carcinogenic effect can be eliminated, continuance of the manufacture and sale of cigarettes "should be seriously questioned."

Palmer ⁷ made similar observations in a consecutive group of 310 male smokers and 112 nonsmokers admitted to a British hospital for elective operations. A diagnosis of bronchitis was based on a history of productive cough for at least two weeks in two consecutive years or by rhonchi or increased density of bronchial markings in the peripheral two-thirds of the lung fields. On this basis, 53.5% of smokers and 30.4% of nonsmokers gave a history of bronchitis, and 32.2% of smokers and 17.9% of nonsmokers showed abnormal physical signs. He made no claim that smoking is the only factor but that it is of substantial importance and "should be discouraged."

Confirmation of the part played by smoking in Great Britain is found in observations of Oswald, who questioned 3,602 men and 2,242 women employed in certain government offices in London as to their smoking habits and the occurrence of bronchitis—chronic cough with sputum and disability—and acute infections. In this group 36% of smokers and 53% of non-smokers were free from symptoms, and 15.9% of smokers and 9.4% of nonsmokers had bronchitis (with disability). The figures in these last

reports are statistically significant.

In the United States, Waldbott,³ stimulated by his own personal experience, studied a series of 31 cases of severe bronchitis in excessive smokers. All complained of cough, wheezing, expectoration, a pharyngitis with mucopurulent discharge, and many also of constriction in the chest, dyspnea or angina-like pains radiating into the neck and arms. He distinguished this "smoker's asthma" from ordinary bronchial asthma by less tendency to wheezing and orthopnea, less involvement of the nose and sinuses, less emphysema, less reduction of the vital capacity, and no evidence of allergy. In the earlier stages, symptoms subsided promptly when smoking was stopped. In some other similar but more advanced cases symptoms did not clear up satisfactorily, and he suggested that this syndrome may be a precursor of some cases of "idiopathic emphysema" and "intrinsic asthma."

Greene 4 reported a study of 4,322 patients coming into two general hospitals for elective operations, with reference to the existence of bronchitis and its relation to smoking. The presence of bronchitis was demonstrated mainly by getting the patient to give one vigorous cough just before anesthesia. Abnormality was indicated by a selfpropagated cough or by "wetness," nearly always found in subjects with a history or signs of tracheobronchial disease and rarely in its absence. Of these subjects 59% of 1,264 men and 26% of 2,068 women were smokers, of whom 79% of the males and 63% of the females smoked heavily—one pack or more a day. Of the

 $^{^7}$ Palmer, K. N. V.: The role of smoking in bronchitis, Brit. M. J. 1: 1473–1474, 1954. 8 Oswald, N. C., et al.: Chronic bronchitis, Lancet 2: 843–844, 1955.

nonsmokers 10.6% showed evidence of bronchitis as compared with 67.4% in all the cigarette smokers. Of the heavy cigarette smokers 82.7% of the men and 76.3% of the women had bronchitis. Pipe and cigar smoking unless inhaled had but little if any tendency to cause bronchitis, and it rarely developed in light smokers. In subjects above 50, other factors become important, but in younger subjects smoking was usually the cause of the bronchitis. Greene found it from four to seven times more frequent than infection as a cause of preoperative bronchitis. In "one pack a day smokers" abstinence of three to four weeks usually cleared up the bronchitis and largely eliminated the postoperative risk of pulmonary complications such as atelectasis and pneumonia. Greene like many others also noted the frequent association of emphysema with "chronic tobacco bronchitis." One might wish that his criteria of bronchitis were less open to subjective bias, but in spite of this the figures are impressive.

Phillips et al.9 studied a series of 18 subjects with severe chronic cough of over 10 years' duration in veterans over 50 who were heavy smokers. All had sputum and all or most had dyspnea, wheezing or rhonchi, and increased anteroposterior diameter of the chest. The maximal breathing capacity and velocity of the air stream were much reduced, and the vital capacity moderately so, features characteristic of emphysema. Bronchoscopic examination confirmed the presence of severe bronchitis macroscopically and by biopsy. He traces the illness as beginning in early adult life with a morning cough with sputum which gradually becomes protracted to occur throughout the day. It is aggravated by frequent acute respiratory infections. As years go by, classical signs of emphysema become evident. Dyspnea appears, at first on exertion, later also when at rest. Pulmonary insufficiency increases, and death may occur from suffocation or right ventricular failure. They stress the diffuse distribution of these changes as shown by biopsies, and the inclusion, in the involvement, of the minute terminal bronchioles, in which secretion and edema of the mucosa cause a proportionally excessive obstruction to the air flow. Distention of the air sacs, atrophy of elastic tissue and loss of elasticity of the lungs occur secondarily in this "obstructive" type of emphysema. Other irritants in sufficient concentration can, of course, cause such a bronchitis, but careful study in this group failed to show any other agent.

To get further evidence as to the cause of chronic cough in various environments, Phillips et al. 10 have recently made a study of the relationship of chronic cough to smoking and to industrial exposures in 1274 males of whom 974 were employed in a large steel-making plant in West Virginia and 300 were selected at random from a Veterans Administration Hospital in Rhode Island. The first group lived in a damp region in which there

⁹ Phillips, R. W., et al.: Chronic bronchitis-a neglected disease entity, Dis. Chest 26:

<sup>520-527, 1954.

10</sup> Phillips, A. M., et al.: Chronic cough: analysis of etiologic factors in a survey of 1274 men, Ann. Int. Med. 45: 216-231, 1956.

was "considerable air pollution" with industrial smoke and gases. They were selected from three departments of the mill. One group in the coke plant worked outside, entirely unprotected from inclement weather and exposed to varying degrees of air pollution with coal dust and coke gas. A second group of masons, engaged in building up and tearing down furnaces of silica brick, were exposed to silica dust and to other nuisance dusts. The third group from the electroplating department was exposed to various irritating fumes including at times hydrofluoric acid. The Veterans Administration Hospital patients were not exposed to such industrial hazards nor to any notable degree of atmospheric pollution. All were studied with reference to the frequency of chronic cough (daily cough with sputum consecutively for a year or more) and its association with the degree of cigarette smoking in each group.

In all, 34% of the 1,274 subjects had a chronic cough. In the mill workers the percentage with cough was nearly the same in each of the three departments, 30 to 34%, whereas in the Veterans Administration group it was 44%. This would suggest that such atmospheric pollution as existed and the unfavorable climatic conditions in the mill were at most minor factors in producing the cough. When analyzed with reference to smoking habits, cough was present in 2% of the 347 who were nonsmokers or pipe or cigar smokers. The proportion with cough among the smokers was closely similar in the three departments, rising from about 20% in the "half pack" and about 50% in the "one pack a day" smokers to 75% or more in the heaviest smokers. The "control" subjects in the Veterans Administration group showed a similar relationship but slightly higher figures.

There was a progressive increase in cough with age in successively higher decades among the smokers, from 38% in the third to 70% in the seventh decade. As the increase at similar ages in nonsmokers was only from 1 to 4%, the increase in the former group seems largely due to the

longer period of exposure to irritation from the smoke.

The authors point out that cigarette smoke is not the only cause of chronic bronchitis, and atmospheric pollution may be important in other specific environments. The work does show that cigarette smoking is a very frequent and potent cause of chronic bronchitis and that industrial air pollution can not be assumed casually to be the cause of pulmonary disease unless the smoking habits of the same group are studied in detail and the effects of smoking duly eliminated.

In a similar independent study, Lowell et al.¹¹ recorded similar observations in 25 unselected patients with chronic obstructive emphysema, 24 heavy cigarette smokers (and one cigar smoker) for over 20 years. All were over 50. In addition to productive cough, they showed increasing

¹¹ Lowell, F. C., et al.: A note on the association of emphysema, peptic ulcer and smoking, New England J. M. 254: 123–124, 1956.

dyspnea and a progressive loss of pulmonary reserve with no notable remissions. The vital capacity was reduced, the residual air (in 11 tested) was more than 50% of the total capacity. The most characteristic feature was slowing of expiration, so that less than 50% of the vital capacity was exhaled in the first second. They believe that this "expirogram" is essential in excluding other causes of dyspnea and that it makes possible recognition of obstructive emphysema in its earlier stages when a positive diagnosis would otherwise be impossible. They stress also the onset of dyspnea after 40, and failure to obtain objective improvement with bronchodilators or steroids, to distinguish this from bronchial asthma.

Although the inflammation undoubtedly must include the larger bronchi, they associate the obstruction with inflammatory changes and relatively marked narrowing of the terminal bronchioles. They suggest that the minute size of the particulate matter in cigarette smoke facilitates its penetration into the smallest airways, whereas the coarser particles of chimney soot, pollen grains and ordinary dusts largely settle out in the larger bronchi where they may cause severe inflammation but less actual obstruction.

They found six cases of peptic ulcer and three of bronchogenic carcinoma among the 25 subjects, diseases which they regard as aggravated or caused

by smoking.

More recently Lowell 12 has reported in greater detail a study of 34 cases of obstructive emphysema and as controls 49 subjects from the wards and outpatient department of the same hospital, unselected except as to age (over 50). The emphysema group included 28 males and six females, all smokers. In the control group there were 23 male smokers and four nonsmokers, six female smokers and 15 nonsmokers. The difference is statistically significant, but the relationship is more striking if the intensity of the smoking is compared. This was estimated by multiplying the average number of packs smoked per day by the duration of the habit in years. The emphysema group had an average record of 47 pack years of smoking, whereas the smokers in the control series averaged 25 pack years. In Lowell's series of 22 males with the requisite data, 77 per cent smoked a pack or more a day. In Hammond and Horn's large series, 13 only 15% of the males from 50 to 70 smoked as much as this. Lowell et al. do not claim that smoking is the only cause of emphysema, but that it is a potent and prolific one. Although they believe that the "association between smoking and carcinoma of the lung" is "established," they point out that emphysema is more common than cancer and when fully developed "has a prognosis almost as gloomy."

These reports offer convincing evidence that heavy smoking of cigarettes over many years is no innocuous procedure. There can be no reasonable

Lowell, F. C., et al.: Chronic obstructive pulmonary emphysema: a disease of smokers, Ann. Int. Med. 45: 268–274, 1956.
 Hammond, E. C., and Horn, D.: The relationship between human smoking habits and death rates, J. A. M. A. 155: 1316–1328, 1954.

doubt that it is a frequent and potent cause of bronchial irritation which, if smoking is continued, often leads to intractable chronic bronchitis and in some cases eventually to obstructive emphysema and fatal pulmonary insufficiency. There is no doubt that other sources of irritation may lead to a similar bronchitis. In some localities irritative dusts associated with industrial activities, the smog of cities like London and Los Angeles, may well overshadow smoking in importance. One might anticipate that the combined action of two such irritants could be exceptionally injurious. Phillips' observations, however, suggest that the relative importance of industrial air pollution in this regard may often have been exaggerated. In fact inhaling hot tobacco smoke into the chest really means bringing in polluted air in higher concentration than would be encountered under almost any other natural conditions.

The relative importance of smoking as an irritant and the frequency with which grave damage follows a resulting protracted bronchitis can be determined precisely only after further observations. Enough is known, however, to indicate the real potential danger. The smoker who does not inhale or who smokes moderately, under 15 cigarettes a day, seems to suffer relatively little except for an occasional hypersensitive subject. Few maintain their smoking at such a level indefinitely, and very few can abstain from inhaling, unconsciously if not deliberately. In the present state of our knowledge it seems our duty as physicians to inform our patients as fully and clearly as possible as to the facts as they are now known and of the potential risks and let them make their own decision, as most of them will do anyway. Positive advice would depend upon the individual's physical condition, his smoking habits and his reaction to smoking. In the presence of chronic pulmonary disease, including established bronchitis, however, complete abstention should be urged without qualification. In any event advice should be based objectively on facts and not swayed by emotional reactions to our own smoking habits and perhaps our reluctance to give up a custom from which much satisfaction and solace may have been obtained.

PAUL W. CLOUGH

REVIEWS

Textbook of Medical Physiology. By ARTHUR C. GUYTON, M.D., Professor and Chairman of the Department of Physiology and Biophysics, University of Mississippi School of Medicine. 1030 pages; 18 × 26 cm. W. B. Saunders Co., Philadelphia. 1956. Price, \$13.50.

This comes close to being the long sought and urgently needed textbook of physiology which can be recommended to medical students with the reasonable hope that their money will be spent on a book they can understand and which will give them the information they need. This happy circumstance arises no doubt from the fact that this is a text written by a single author whose experience in the lectu. e halls, student laboratories, and conference rooms has been broad enough to give him a thorough understanding and appreciation of the needs and capabilities of the freshman medical student. It is unusual nowadays for one individual to have the temerity to assume such a burden but in this instance it has paid off handsomely.

There is nothing unusual about its contents and the subject is treated in the conventional way. However, the text is lucid, the charts simple and understandable. They are redrawn for the most part from originals published elsewhere. As a rule the illustrations are all line drawings thus eliminating those fuzzy, blurred and generally confusing photographs which have marred more than one physiology text in the past. There is excellent correlation between the pathological and the normal and the two

are skillfully inter-mixed so that they illuminate each other.

No textbook of physiology has ever been written nor ever will be written which does not contain somewhere statements which will be challenged by somebody. This book is no exception. However, controversial material is kept to a minimum and the student's attention focused on what is generally held to be basic. The expanding boundaries of the subject have been recognized and chapters on high and low pressure physiology, as well as the effects of radiation have been included. There is an excellent although somewhat brief chapter on the maintenance of the internal environment and the concept of homeostasis which serves to give the student a reasonably good philosophical orientation. Well chosen bibliographies at the end of each chapter are perhaps one of the most useful features of the book for the serious student. All in all the clinician who is looking for a physiology text to bring him abreast of this growing subject could do no better than to choose this one.

DIETRICH C. SMITH, M.D.

Histamine: Ciba Foundation Symposium Jointly with the Physiological Society and the British Pharmacological Society, in Honour of Sir Henry Dale, O.M., G.B.E., M.D., F.R.C.P., F.R.S. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. 472 pages; 14 × 21 cm. Little, Brown & Co., Boston. 1956. Price, \$9.00.

In April, 1955, scientists from many lands gathered in London to participate in two symposia on histamine in honor of Sir Henry Dale, a pioneer in investigations on this physiologically important substance. One symposium, sponsored jointly by the Physiological and Pharmacological Societies held at The Wellcome Foundation, was attended by many members of the sponsoring societies, while the second, the Ciba Foundation Symposium, was attended only by a small group of invited investigators who are well known for their work on histamine. This book is a record of the two symposia.

Histamine has been of great interest to scientists since its isolation from ergot in 1910 and the early demonstration by Barger and Dale of its occurrence in intestinal mucosa. The later work of Abel and many others demonstrating its presence in practically all body tissues aroused further interest. The role of histamine in anaphylactic and other shock-like states, allergic reactions, and biochemical processes has been the subject of countless research projects ever since. With the development of modern biochemical technics, as illustrated in so many papers in this volume, striking advances in our knowledge of histamine have taken place, and even greater advances may be anticipated for the future.

The volume is divided into two sections: Section I, The Symposium of The Physiological and Pharmacological Societies at the Wellcome Foundation; and Section II, The Symposium at the Ciba Foundation. The first section contains 35 papers and short communications, and the second consists of 9 papers and a general discussion of the present state of histamine research and some speculations about the future. Broad topics considered at both symposia were: the occurrence, origin, mechanism of release, significance and fate of histamine in the body. A valuable feature of the Ciba Symposium is a verbatim transcription of the discussion following each paper, which gives the reader an opportunity to profit by the vast range of topics discussed and to experience vicariously the enthusiasm manifested by a group of dedicated investigators.

This book is undoubtedly the most comprehensive work on histamine available at the present time and summarizes our current knowledge of this ubiquitous and fascinating amine. The reader is presented with a picture of a rapidly advancing frontier of fundamental research on a substance of great importance in the dynamics of living organisms, and to those interested in fundamental biochemical, physiological and pharmacological processes this book will be of great interest and is enthusiastically recommended by the reviewer.

RAYMOND M. BURGISON, Ph.D.

Clinical Hematology. 4th Ed. By Maxwell M. Wintrobe, M.D., Ph.D. 1184 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1956. Price, \$15.00.

The fourth edition of this textbook appears five years after its predecessor and includes numerous changes to keep pace with new ideas. There has been revision of much of the text as well as the addition of two new chapters—one on blood groups and blood transfusion and another on abnormal hemoglobin syndromes. Everywhere there is the mention of recent work and the inclusion of valuable new references.

This book continues to be outstanding in its field. It is notable for its clarity and completeness of coverage of the broad aspect of medicine which now comprises hematology. Of course, as with any text covering a wide area, there are subjects about which the reader will need to look elsewhere for more specific details. On the whole, however, there is meticulous attention to detail—both clinical and laboratory—with extensive documentation of information. The bibliography which follows each section is accurate, pertinent, and extremely valuable.

As a reference for the internist and the internist specializing in hematology, this

book is heartily recommended.

A. B.

Differentialdiagnose innerer Krankheiten. 4th Ed. By ROBERT HEGGLIN. 678 pages; 17.5 × 24.5 cm. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corp., N. Y. 1956. Price, Ganzleinen DM 69.60.

Books on differential diagnosis covering all of internal medicine present a great problem to the author because of the enormous volume of facts known. Differential diagnostics is within the realm of postgraduate education and requires of the author experience in clinical medicine, a great breadth of knowledge and teaching ability. Dr. Hegglin's success in this formidable task is evidenced by the appearance of a fourth edition of his book, as well as an Italian and a Spanish translation.

The book is well-balanced, though a little over-emphasis of pet subjects is noticeable. So, for instance, dye-dilution curves for the diagnosis of veno-arterial shunts are of interest but hardly of differentiating value. Pulmonary arteriovenous aneu-

rysms are not encountered as the cause of cyanosis in pulmonic stenosis.

The discussion throughout is at a very high level and presented very clearly. The book is based on a solid knowledge of diseases. The 372 illustrations are well chosen and supplement the text well. For those having a reading knowledge of German this volume offers a valuable discussion of differential diagnosis.

A. G

Progress in Clinical Obstetrics and Gynaecology. By T. L. T. Lewis, M.B., B.Chir. (Camb.), F.R.C.S. (Eng.), M.R.C.O.G. 594 pages; 16 ×24.5 cm. Little, Brown and Company, Boston. 1956. Price, 12.00.

This British volume is an excellent condensation of clinical advances made in Obstetrics and Gynecology during the past 10 to 15 years. The author has presented the material without bias, but has added materially to the value of the volume by his

own personal views on many conflicting issues.

In obstetrics such new discoveries as the effects of rubella, post-maturity, retrolental fibroplasia, hyaline membrane disease, and kernicterus, all conditions intimately associated with infant mortality and morbidity, are discussed. Other new concepts such as amniotic fluid embolism, afibrinogenemia, the problems of the pre-diabetic, hormone therapy in the pregnant diabetic, pitocin infusion in uterine inertia are presented and evaluated.

In the field of gynecology recent advances in the therapy of carcinoma of the cervix, both radiologically and surgically, the early diagnosis of carcinoma by cytological diagnosis are thoroughly discussed. Malignant disease of the ovary, vulva

and the body of the uterus are similarly treated.

Pelvic tuberculosis with especial reference to chemo-therapy; operations for stress incontinence and the newer concepts of endocrinology and endocrinologic ther-

apy are presented.

This review may well be better termed Recent Advances in Obstetrics and Gynecology in the British Empire. References from other countries are sparse. In all fairness, however, more references would only add more completeness, but not material.

The book can be recommended to all physicians for compact, easy-to-read, and up-to-date postgraduate reading in obstetrics and gynecology. It is of course not a textbook and many subjects are omitted, since new advances have not been made in all fields.

D. FRANK KALTREIDER, M.D.

Treatment of Heart Disease: A Clinical Physiologic Approach. By Harry Gross, M.D., F.A.C.P., and Abraham Jezer, M.D. 549 pages; 17 × 26 cm. W. B. Saunders Company, Philadelphia. 1956. Price, \$13.00.

With the large number of new books on Cardiology, it is not surprising to find that the authors of this text attempt to justify the publication of yet another. They do this ably in a preface, when they state that ". . . It is a presentation of therapy in heart disease based upon sound physiologic principles." The contents include sections devoted to the basic mechanisms of cardiac symptoms and their management, hypertensive heart disease and arteriosclerotic heart disease, diseases of the heart secondary

to inflammation, congenital heart disease, surgery in the cardiac patient, diseases of the heart secondary to metabolic disorders, and emotions, adjustments, and rehabilitation in heart disease.

The authors write in a clear, lucid manner. It is a scholarly text, with not only an adequate evaluation of the literature but with the authors' own experiences and therapeutic suggestions. Although one may differ with some details of management, there is always an attempt to justify suggestive therapy on the basis of sound physiologic principles. The text should prove invaluable to anyone interested in the treatment of heart disease.

L. S

BOOKS RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Alcoholism. Edited by George N. Thompson, A.B., M.D., F.A.C.P., Associate Clinical Professor of Neurology and Psychiatry, School of Medicine, University of Southern California, Los Angeles, California, etc. 548 pages; 24 × 15.5 cm. 1956. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$9.50.
- Die Behandlung des Bluthochdruckes. By Prof. Dr. L. Hantschmann, 92 pages; 24 × 17 cm. (paper-bound). 1956. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, kartoniert DM 12.—
- Clinical Chemistry: Principles and Procedures. By Joseph S. Annino, Clinical Chemist, Massachusetts Memorial Hospitals, Boston, Massachusetts. 280 pages; 24 × 16 cm. 1956. Little, Brown and Company, Boston. Price, \$7.50.
- Dermatology. By Donald M. Pillsbury, M.A., D.Sc. (Hon.), M.D., Professor and Director of Department of Dermatology, University of Pennsylvania School of Medicine, etc.; Walter B. Shelley, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine, etc.; and Albert M. Kligman, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine, etc. 1,331 pages; 25.5 × 17 cm. 1956. W. B. Saunders Company, Philadelphia. Price, \$20.00.
- Diabetes-Komplikationen: Eine klinische Studie. By Doz. Dr. Alfred Kaeding. 146 pages; 24.5 × 16 cm. 1956. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 28.-; ganzleinen DM 30.-
- Die Erkrankungen der Gallenwege. By Dr. Wilhelm Schöndube. 311 pages; 24.5 × 16.5 cm. 1956. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 44.-; ganzleinen DM 47.-
- Group Processes: Transactions of the Second Conference, October 9, 10, 11 and 12, 1955, Princeton, N. J. Edited by Bertram Schaffner, M.D., University Seminar on Communications, Columbia University, New York, N. Y. 255 pages; 23.5 × 16 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$3.50.
- Internal Medicine: A Physiologic and Clinical Approach to Disease. By ROBERT P. McCombs, B.S., M.D., F.A.C.P., Professor of Graduate Medicine, Tufts University School of Medicine, etc. 706 pages; 23.5 × 15.5 cm. 1956. The Year Book Publishers, Inc., Chicago. Price, \$10.00.

- The Labyrinth: Physiology and Functional Tests. By Joseph J. Fischer, M.D., Clinical Professor in Otolaryngology, School of Medicine, Tufts University, etc. 206 pages; 23.5 × 15.5 cm. 1956. Grune & Stratton, New York. Price, \$6.00.
- A Manual of the Common Contagious Diseases. 5th Ed. By Philip Moen Stimson, A.B., M.D., Professor of Clinical Pediatrics, Cornell University Medical College, etc.; and Horace Louis Hodes, A.B., M.D., Pediatrician-in-Chief and Director of the Department of Pediatrics, Mt. Sinai Hospital, New York City, etc. 624 pages; 20 × 13.5 cm. 1956. Lea & Febiger, Philadelphia. Price, \$8.50.
- Masked Epilepsy. By Hugh R. E. Wallis, B.A., M.D., M.R.C.P., D.C.H., Consultant Paediatrician, Bath Clinical Area, etc. 51 pages; 22.5 × 14 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, \$2.50.
- Nerve Impulse: Transactions of the Fifth Conference, September 20, 21 and 22, 1954, Princeton, N. J. Edited by David Nachmansohn, M.D., Professor of Biochemistry, Columbia University College of Physicians and Surgeons, New York, N. Y.; and H. Houston Merritt, M.D., Professor of Neurology, Columbia University College of Physicians and Surgeons, New York, N. Y. 256 pages; 23.5 × 16 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$4.50.
- Observations on Krebiozen in the Management of Cancer. By A. C. Ivy, Ph.D., M.D., Distinguished Professor of Physiology and Head of the Department of Clinical Science, University of Illinois, etc.; John F. Pick, S.B., M.M., M.D., Head of Department of Plastic Surgery, Columbus Hospital, Chicago, etc.; and W. F. P. Phillifs, M.D., Department of General Practice, St. Francis Hospital, Evanston, Illinois. 107 pages; 22 × 14.5 cm. 1956. Henry Regnery Company, Chicago. Price, \$2.50.
- Der Rheumatismus. Beiträge von R. Hopmann, A. Goebel, H. Ewerbeck, O. Guthof, L. B. Seiferth, K. Fr. Schmidhuber, B. Schuler and M. Hackenbroch; herausgegeben von Prof. Dr. R. Hopmann. 99 pages; 24 × 17 cm. (paper-bound). 1956. Georg Thieme Verlag, Stuttgart. Price, kartoniert DM 16.50.
- Roentgen Signs in Clinical Diagnosis. By Isadore Meschan, M.A., M.D., Professor and Director of the Department of Radiology at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina, etc.; with the assistance of R. M. F. Farrer-Meschan, M.B., B.S. (Melbourne, Australia). 1,058 pages; 26 × 17 cm. 1956. W. B. Saunders Company, Philadelphia. Price, \$20.00.
- Symposium on the Role of Some of the Newer Vitamins in Human Metabolism and Nutrition: Proceedings of the Nutrition Symposium Held at Vanderbilt University School of Medicine, Nashville, Tennessee, October 20-21, 1955. Nutrition Symposium Series Number 12. By R. D. Adams, W. B. Bean, B. F. Chow, D. B. Coursin, Kate A. Daum, P. L. Day, J. S. Dinning, G. D. Duncan, H. H. Gordon, L. D. Greenberg, P. György, P. L. Harris, C. C. Harvey, A. E. Hellinger, A. Horonick, M. K. Horwitt, R. Lubin, K. E. Mason, E. W. McHenry, H. M. Nitowsky, K. Okuda, J. F. Rinehart, J. T. Tildon, D. B. Tower, M. Victor, R. W. Vilter, M. Wachstein and W. C. Wilson. 137 pages; 26.5 × 19.5 cm. 1956. The National Vitamin Foundation, Incorporated, New York. Price, \$2.50.

COLLEGE NEWS NOTES

New A.C.P. LIFE MEMBERS

The College acknowledges with pleasure the following Fellows as Life Members:

Dr. Milton H. Robbins, New York, N. Y. Dr. Samuel T. Schlamowitz, Syracuse, N. Y.

GIFTS TO COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College gratefully acknowledges receipt of the following books by members of the College for the Memorial Library of the College:

Alvan L. Barach, M.D., F.A.C.P., New York, N. Y., Pulmonary Emphysema, written in collaboration with Hylan A. Bickerman, M.D., F.A.C.P., published by The Williams & Wilkins Company, Baltimore, 1956; Illustrated, 545 pages.

John H. Bland, M.D., F.A.C.P., Burlington, Vt., Clinical Recognition and Management of Disturbances of Body Fluids, 2nd Edition, published by W. B. Saunders Company, Philadelphia, 1956; Illustrated, 522 pages.

Hervey Cleckley, M.D., F.A.C.P., Augusta, Ga., The Mask of Sanity, 3rd Edition,

published by The C. V. Mosby Company, St. Louis, 1955; 596 pages.

Mahlon H. Delp, M.D., F.A.C.P., Kansas City, Kans., Physical Diagnosis, 5th Edition, written in collaboration with Ralph H. Major, M.D., published by W. B.

 Saunders Company, Philadelphia, 1956; Illustrated, 358 pages.
 H. Corwin Hinshaw, M.D., Ph.D., F.A.C.P., San Francisco, Calif., and L.
 Henry Garland, M.B., B.Ch., San Francisco, Calif., Diseases of the Chest, published by W. B. Saunders Company, Philadelphia, 1956; Illustrated, 727 pages.

Edgar Mayer, M.D., F.A.C.P., New York, N. Y., Pulmonary Carcinoma, written in collaboration with Herbert C. Maier, M.D., published by New York University Press, Washington Square, New York, distributed by J. B. Lippincott Company, Philadelphia, New York, 1956; Illustrated, 540 pages.

Karl Menninger, M.D., F.A.C.P., Topeka, Kans., A Guide to Psychiatric Books, published by Grune and Stratton, New York, 1956; 157 pages.

A.C.P. CREDENTIALS MEETING

The Committee on Credentials will hold a meeting at Philadelphia, March 9-10, 1957, and at Boston, April 5-6, immediately preceding the Board of Regents Meeting on April 6-7, 1957.

Proposals for Advancement to Fellowship and/or new members to be acted upon at these meetings, must be received at College headquarters sixty days in advance of these dates. Governors may require that proposals be in their hands 90 days before the meetings.

SCHEDULE OF COMING A.C.P. REGIONAL MEETINGS, 1957

		M.D.,		M.D.,	M.D.,	M.D.,	M.D.,	M.D.,	M.D.,
Official Guest	E. R. Loveland	Walter L. Palmer, M.D., President		Richard A. Kern, M.D., President-Elect	Richard A. Kern, M.D., President-Elect	Walter L. Palmer, M.D., President	Howard P. Lewis, M.D., Regent	Richard A. Kern, M.D., President-Elect	Richard A. Kern, M.D., President-Elect
Governor and/or Chairman	John Minor, M.D. R. Carmichael Tilghman, M.D.	Charles A. Doan, M.D. Homer D. Cassel, M.D., Chairman	Thomas M. McMillan, M.D.	C. F. Kemper, M.D. C. Wesley Eisele, M.D., Chairman	Lemuel C. McGee, M.D. Ward W. Briggs, M.D., Chairman	Carl V. Moore, M.D.	George C. Griffith, M.D. Harry E. Henderson, M.D., Chairman	Charles M. Caravati, M.D.	William C. Menninger, M.D. Samuel Zelman, M.D., Chairman
Territory	District of Columbia- Maryland	Ohio	Eastern Pennsylvania	Colorado	Delaware	Missouri	Southern California	Virginia	Kansas
City	Washington, D. C.	Dayton	Philadelphia	Colorado Springs	Wilmington	St. Louis	Santa Barbara	Williamsburg	Topeka
Date	Jan. 12	Jan. 17	Jan. 18	Jan. 18–19	Feb. 9	Feb. 23	Feb. 23-24	March 2	March 15

American College of Physicians Post-Convention Tour—1957

Following the Annual Session of the College at Boston, Mass., April 8-12, 1957, there will be a post-Convention Tour to Puerto Rico, St. Thomas, Dominican Republic, and Haiti, under the management of Mr. Joseph Sims, House of Travel, 1600 Walnut St., Philadelphia, Pa.

The itinerary is as follows:

Fri. April 12	Cocktail Party at the Statler Hotel	6:20
		6:30 p.m.
Sat. April 13	Leave Boston by special flights via P.A.A. Arrive San Juan (7 hour flight)	a.m. p.m.
	Reception at Airport and transfer to La Rada Hotel Presidential Cocktail Party	7:00 p.m.
Sun. April 14	One half of our group will fly to St. Thomas for sight- seeing, shopping and lunch, returning to San Juan in the late afternoon One half of our group will go to El Yunque National Rain Forest and Luquillo Beach and lunch	a.m.
Mon. April 15	American College of Physicians scientific program American College of Physicians Banquet	
Tues. April 16	Same as April 14	a.m.
Wed. April 17	Fly to Ciudad Trujillo, Dominican Republic Transfer to the Hotel Embajador	a.m.
	Sightseeing and inspection of Hospitals	p.m.
Thurs. April 18	Drive to Boca Chica for lunch and Isle of Matica Dinner at Hotel.	a.m.
Fri. April 19	Fly to Port au Prince, Haiti. Hotel Riviera	a.m.
	Sightseeing, including Kenscoff Mt. Cocktail Party and Reception	p.m
Sat. April 20	Drive to Albert Schweitzer Memorial Hospital for inspection and lunch	a.m.
Sun. April 21	Departure for New York or Miami by air	a.m.
Mon. April 22	Those desiring to return by ship may sail on the S.S. Ancon of the Panama Line	
Fri. April 26	S.S. Ancon arrives in New York	

LAND ARRANGEMENTS: Include Superior twin-bedded rooms and bath.

Hotels: La Rada, San Juan, Puerto Rico, European Plan

El Embajador, Ciudad Trujillo & La Riviera, Port au Prince, breakfast and dinner.

Transfer from airport to Hotel from arrival San Juan throughout

Sightseeing as indicated on the itinerary.

Entertainment as indicated on the itinerary.

Tourist cards for Dominican Republic and Haiti.

Requirements—Proof of citizenship and smallpox vaccination certificate.

A.C.P. POSTGRADUATE COURSES

Courses Already Concluded

- Course No. 1, Recent Advances in Cardiovascular Diseases: Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., co-directors; The Mt. Sinai Hospital, New York, N. Y. This course was over-subscribed even after the directors permitted a registration of 210; a most popular course, backed up with superior content and teaching staff.
- Course No. 2, Seminars in Internal Medicine: Rudolph H. Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., M.A.C.P., co-directors; Vanderbilt University School of Medicine, Nashville, Tenn. An extremely popular course of superior content and faculty; greatly oversubscribed, even with the maximal raised 15%.
- Course No. 3, Clinical Neurology: Bernard J. Alpers, M.D., F.A.C.P., director; Jefferson Medical College of Philadelphia. A very satisfactory registration, although not up to maximal capacity, due to the smaller number of members of the College who are especially interested in Clinical Neurology; those registered give extremely favorable comments.

At the time this News Note is being prepared, registration is not yet complete for Course No. 4, Recent Advances in Internal Medicine: Robert H. Williams, M.D., F.A.C.P., director; University of Washington School of Medicine, Oct. 22–26; Course No. 5, Selected Problems in Internal Medicine: Stewart G. Wolf, Jr., M.D., F.A.C.P., director; University of Oklahoma School of Medicine; Nov. 26–30; Course No. 6, Gastroenterology: Henry L. Bockus, M.D., F.A.C.P., director; University of Pennsylvania Graduate School of Medicine; Dec. 3–7. However, it is quite apparent that Course No. 4 will be over-subscribed, Course No. 5 well attended, and Course No. 6 very greatly over-subscribed.

The remaining two courses, No. 7, Electrocardiography: Hans H. Hecht, M.D., director; University of Utah College of Medicine, and Course No. 8, Pathologic Physiology of the Blood Dyscrasias: Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., (Associate), and Edward H. Reinhardt, M.D., (Associate), codirectors; Washington University School of Medicine, St. Louis, are still open for registration. Course No. 7 takes place Dec. 3–8, and Course No. 8, Feb. 18–22, 1957. These are two excellent courses that should not be overlooked by registrants. Outlines are available on request to the Executive Offices of the College, 4200 Pine St., Philadelphia 4, Pa.

The Committee on Postgraduate Courses met at the College headquarters on November 10, and announcement will be made in the next issue of this JOURNAL of the proposed courses for the Spring of 1957.

THE WEST VIRGINIA REGIONAL MEETING

The West Virginia Regional Meeting was held at Charleston, W. Va., Sept. 29, 1956, under the Governorship of Dr. Paul H. Revercomb and the Program Committee headed by Dr. Richard N. O'Dell. Dr. Wallace M. Yater, F.A.C.P., Secretary General of the College, was the banquet speaker in the evening at the Edgewood Country Club.

Heretofore, the West Virginia Regional Meeting had been held during the meeting of the West Virginia State Medical Association. This year it was a separate and distinct meeting, conflicting with no other medical activity in the state. The results were gratifying; a larger percentage of the College members of the State were in attendance, and the program was put on by a number of the Associates of the College, interspersed with Fellows and guests. The attendance was gratifying in large measure, except for poor representation from one of the larger cities of West Virginia. While many Associates of the College were in attendance, a sizeable number failed to come. The Committee on Credentials puts considerable emphasis on Associates participating in the Regional Meetings, and it is hoped that all Associates will attend their State's Regional Meeting in the future.

Tentatively, it is planned to hold the 1957 Regional Meeting at Wheeling, W. Va., and Dr. W. R. Sheppe, F.A.C.P., has been appointed Chairman of the Program Committee.

SYMPOSIUM ON IMMUNOLOGY

The Milwaukee Academy of Medicine will conduct a Symposium on Immunology at Marquette University, Brooks Memorial Union, on Saturday, December 1, 1956.

Among those appearing on the Faculty are Dr. Carl V. Moore, F.A.C.P., Professor of Medicine at Washington University School of Medicine, St. Louis, and College Governor for The American College of Physicians representing Missouri, and Dr. Theodore L. Squier, F.A.C.P., Associate Clinical Professor of Medicine at Marquette University School of Medicine.

All physicians are welcome to attend. There will be no registration fee. Reservations may be made by writing to the Milwaukee Academy of Medicine, 561 North Fifteenth Street, Milwaukee 3. Programs also are available upon request.

AMERICAN BOARD OF NUTRITION

The American Board of Nutrition will hold the next examinations for certification as a Specialist in Human Nutrition, in April 1957, at Chicago, Illinois. Candidates who wish to be considered for these examinations should forward applications to the Secretary's office not later than March 1. Application forms may be obtained from the Secretary, Otto A. Bessey, Environmental Protection Research Division, Quartermaster Research and Development Center, Natick, Massachusetts.

New York University will offer a two-week, full-time course in Radiological Safety from January 7 to 18, 1957, at the Institute of Industrial Medicine, in cooperation with the New York University College of Engineering and the United States Atomic Energy Commission. The course is designed for industrial physicians, industrial hygiene engineers, public health officials, and individuals in industrial and university research laboratories who are responsible for radiological safety.

Information may be obtained from the Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N. Y.

SECOND WORLD CONFERENCE ON MEDICAL EDUCATION

Under the auspices of the World Medical Association, the Second World Conference on Medical Education will be held at Chicago, Ill., August 30-September 4, 1959. The theme will be "Medicine—Life Long Study." The objective is the exchange of information for the purpose of assisting in raising the standards of medical education of the world.

Dr. Raymond B. Allen, F.A.C.P., Chancellor, University of California at Los Angeles will be President, and Dr. Victor Johnson, F.A.C.P., Director of the Mayo Foundation for Medical Education and Research, University of Minnesota Graduate School, will be the Deputy President.

NEW APPOINTMENTS TO THE AMERICAN BOARD OF INTERNAL MEDICINE

Dr. Thomas Almy, F.A.C.P., Director of The Cornell Medical Service, Bellevue Hospital, New York City, has been elected a member of the American Board of Internal Medicine as a representative of the American Medical Association to replace Dr. Claude E. Forkner, F.A.C.P.

Dr. Frank B. Kelly, F.A.C.P., of Chicago, Illinois, and Dr. A. Carlton Ernstene, F.A.C.P., of Cleveland, Ohio, were elected members of the Sub-specialty Board in Cardiovascular Disease for a term of five years beginning July 1, 1956. Drs. Kelly and Ernstene replaced Drs. Howard Wakefield, F.A.C.P., and Willard R. Wirth, F.A.C.P., whose terms expired July 1, 1956.

Dr. C. Wilmer Wirts, F.A.C.P., Philadelphia, was elected a member of the Subspecialty Board in Gastroenterology for a term of five years beginning July 1, 1956, to replace Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, Canada, whose term expired at that time.

THE UNIVERSITY OF PENNSYLVANIA GRADUATE SCHOOL OF MEDICINE

The Graduate School of Medicine of the University of Pennsylvania is the only distinct graduate school not attached to or directly affiliated with the school of medicine of a university. This School has a separate identity from the Medical School of the University of Pennsylvania and offers full-time courses in the basic sciences and extending through the various specialties. The full one-year course provides only a certificate but the longer courses lead to the degree of Master of Science in Medicine. Dr. George Morris Piersol, M.A.C.P., is the Dean.

250 students are registered for the 1956-57 session. Of these 39 are registered in internal medicine, the largest specialty group in the School. 131 registrants are from the United States and its territories. Many foreign countries are represented.

Cornerstone laying ceremonies for a fifteen-story Hall of Residence at New York University-Bellevue Medical Center were held on September 26, 1956, at 30th Street and the East River Drive, New York City. Dr. George E. Armstrong, F.A.C.P., is Vice President for Medical Affairs of New York University and Director of the Medical Center.

The Hall of Residence is scheduled to be completed by December of this year with occupancy beginning in January 1957. The building will accommodate 366 students of the Medical Center and 30 students from the College of Dentistry. Funds were raised totaling over one million dollars for student housing, equipment and related facilities. A substantial gift was received from the Samuel H. Kress Foundation and many contributions were received from friends and associates of

the Medical Center. An additional \$1,650,000.00 was made available through a Government loan under the Housing and Home Finance Agency as a College Housing Loan under Title IV of the Housing Act.

This is the fourth main building to be constructed of a \$32,000,000.00 development program. Completed are: The Institute of Physical Medicine and Rehabilitation, the Medical Science Building, and the Henry W. & Albert A. Berg Institute for Experimental Physiology, Surgery and Pathology. Alumni Hall Auditorium and Lecture Rooms is scheduled for occupancy in September 1957. A new University Hospital, now in the planning stage, will complete the Medical Center program.

THE NATIONAL FOUNDATION FOR INFANTILE PARALYSIS OFFERS POSTDOCTORAL FELLOWSHIPS

The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y., announces a series of fellowships for postdoctoral study, including a research fellowship in medicine and related biological sciences, and others in the clinical fields of preventive medicine, rehabilitation, orthopedics, psychiatry, and management of poliomyelitis. Details may be obtained from the headquarters of the Foundation.

Dr. Walter L. Palmer, F.A.C.P., President of the American College of Physicians, addressed the Second National Congress of Medicine, University of Chile, Santiago, South America, October 3–8, 1956. Dr. Palmer spent a month touring medical centers in South America. Others on the program of the Second National Congress of Medicine included Dr. Joseph L. Hollander, F.A.C.P., Philadelphia, and Dr. Tinsley R. Harrison, F.A.C.P., Birmingham.

Dr. Monroe J. Romansky, F.A.C.P., Washington, D. C., has been elected President of the Jacobi Medical Society.

Dr. Ross T. McIntire, F.A.C.P., Executive Director of the International College of Surgeons, was recently honored by President Eisenhower in recognition of his outstanding work in organizing and developing the President's Committee on Employment of the Physically Handicapped.

Dr. George F. Schmitt, F.A.C.P., Miami, Fla., is parliamentarian for the Florida State Association of the National Association of Parliamentarians. Dr. Schmitt has also been appointed to the Advisory Board of the Alumni Association of the Mayo Foundation.

Dr. Schmitt (30 Southeast Eighth St., Miami 32, Florida), has published in a concise form charts of parliamentary procedure, and will furnish copies to any reader who is interested.

Dr. Howard C. Coggeshall, F.A.C.P., has been elected President of the Dallas Southern Clinical Society. Their next Spring meeting will be held March 17-20, 1957, at the Statler-Hilton Hotel, Dallas, Texas. Drs. Tinsley R. Harrison, F.A.C.P., and Wesley W. Spink, F.A.C.P., will be honor guests on the program.

The Third Annual Meeting of the Academy of Psychosomatic Medicine was held in New York City, October 4-6, 1956. A panel on "Obesity-A Psychosomatic

Dilemma," had among its participants Dr. Norman Jolliffe, F.A.C.P., Director of Nutrition, City of New York Health Department, and Associate Professor of Nutrition, Columbia University; Martin J. Goldner, M.D., F.A.C.P., Clinical Professor of Medicine, State University of New York College of Medicine, and Director of Medicine, Jewish Chronic Disease Hospital of Brooklyn; and Wilfred Dorfman, M.D., F.A.C.P., a member of the medical staffs of Maimonides and Coney Island Hospitals, and of the psychiatric staff of the Brooklyn State Hospital, who served as moderator.

Other participants on the program included Dr. George J. Train, F.A.C.P., "Flight Into Health—A Pitfall in the Evaluation of Therapeutic Results"; Irving J. Sands, M.D., F.A.C.P., "General Practice—Where the Psyche Meets the Soma"; Dr. M. Murray Peshkin, F.A.C.P., moderated a panel discussion on "Psychosomatic Aspects of Allergic Diseases."

Dr. Dorfman was elected to the post of Historian for the ensuing year. He will continue as a member of the Executive Council and as Chairman of the Public Education Committee. Dr. Peshkin will also continue as a member of the Executive Council.

Three Fellowships for study or research in the medical sciences or in the basic sciences which contribute to the advancement of human health, are available at the Montefiore Hospital, Pittsburgh, Pa. The Committee will consider applicants for the Fellowships not only on the basis of high scholastic standing, but also on aptitude for research, without limiting the selection of Fellows to residents of any area, and without regard to race, color, creed, or religion. Interested persons desiring information may write to Bessie Frank Anathan Fellowship Fund, The Montefiore Hospital, Fifth Avenue at Darragh St., Pittsburgh 13, Pa.

The University of Michigan Medical School sponsored a meeting at the University on October 11, at which several leading medical scientists of the country participated in a program discussing unsolved problems of how the body is able to use vitamins and other foodstuffs to make energy and tissue. Dr. Frank H. Bethell, F.A.C.P., was Chairman, and participants came from various universities throughout the country. Dr. Jerome W. Conn, F.A.C.P., of the University of Michigan, presented a report on "Primary and Secondary Aldosteronism."

The Association of Teachers of Preventive Medicine held its Thirteenth Annual Meeting at Atlantic City, N. J., November 11, 1956, under the Presidency of Dr. Duncan W. Clark, (Associate). The afternoon program was given over to a series of round tables. Dr. Clark, Professor and Chairman of Environmental Medicine and Community Health, State University College of Medicine at New York City, Dr. John P. Hubbard, F.A.C.P., Professor and Chairman of Public Health and Preventive Medicine at the University of Pennsylvania School of Medicine, and Dr. George Reader, F.A.C.P., Director of the Comprehensive Care and Teaching Program at Cornell University Medical College, were among the panelists. Dr. John R. Paul, F.A.C.P., Professor of Preventive Medicine at Yale University School of Medicine, New Haven, addressed the dinner session on "Experiences in the Soviet Union."

"The Borderlines of Cancer" was depicted in a 90-minute program of live closed-circuit telecasts on the evening of October 17, 1956, from Tufts University School of Medicine and the New England Medical Center in Boston. This was the third in the "Grand Rounds" series, and is provided to the medical profession through

the Upjohn Company. Among the guest clinicians were Dr. Edwin B. Astwood, F.A.C.P., of Boston, and Dr. Henry L. Bockus, F.A.C.P., Professor and Chairman of the Department of Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia. Dr. Alexander Marble, F.A.C.P., of Boston, participated in a presentation on oral hypoglycemic agents.

"Step Lively . . . and Lose Weight" is the title of a simple and safe guide for weight reduction, published by the American Dietetic Association, 620 N. Michigan Ave., Chicago 11, Ill.

The Medical Society of Virginia conducted its Annual Meeting at Roanoke, Va., October 14-17, 1956. Among the invited guests were Dr. Francis Braceland, F.A.C.P., President of the American Psychiatric Association, Hartford, Conn., and Dr. E. E. Menefee, Jr., F.A.C.P., Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.

Dr. Harry Walker, F.A.C.P., Professor of Clinical Medicine at the Medical College of Virginia, is now Acting Chairman of the Department of Medicine during the incapacitation of the Chairman, Dr. William B. Porter, F.A.C.P.

The Virginia Trudeau Society held its meeting at Richmond, Va., Sept. 26. Among their featured speakers were Dr. Esmond R. Long, M.A.C.P., former Director of Medical Research for the National Tuberculosis Association and former Head of the Henry Phipps Institute of Philadelphia, and Dr. Julius Wilson, F.A.C.P., Director of the National Tuberculosis Association Medical Education Division. Dr. E. S. Ray, F.A.C.P., of the Medical College of Virginia, was a panelist on "Home Treatment of Pulmonary TB Versus Sanatorium Treatment."

Recently the American Heart Association renewed its grants for heart research for investigation being pursued by Dr. Reno Porter, F.A.C.P., of the Medical College of Virginia.

SCHOLARSHIPS FOR POSTGRADUATE EDUCATION IN PUBLIC HEALTH PROPOSED

Announcement was recently made that a bill will be presented to Congress proposing "to amend the Public Health Service Act to provide a program of scholarships for postgraduate education." The bill would provide \$250,000 annually for five years. The Surgeon General of the Public Health Service would be instructed to determine the need for scholarships in each field relating to Public Health. The awards would include the cost of maintenance, tuition, equipment and books.

Dr. Robert C. Hardin, F.A.C.P., State University of Iowa College of Medicine, Iowa City, has received a training grant of \$8,000 a year for five years from the Institute of Arthritis and Metabolic Diseases, National Institutes of Health, for long-term follow-up of patients with diabetes.

Dr. Lawrence Reynolds, F.A.C.P., Professor of Radiology, was a recipient of the honorary degree of Doctor of Laws at the last commencement exercises of Wayne University, Detroit.

Dr. Louis H. Clerf, F.A.C.P., Emeritus Professor of Bronchoesophagology and Laryngology at Jefferson Medical College of Philadelphia, received the 33rd Annual Strittmatter Award of the Philadelphia County Medical Society recently. Dr. Clerf is a former President of that Society.

Dr. Sol Katz, F.A.C.P., and Dr. Howard M. Payne, (Associate), both of Washington, D. C., addressed the 36th Annual Meeting of the West Virginia Tuberculosis and Health Association at Beckley, W. Va., September 13–14.

The Hematology Research Foundation, 64 W. Randolph St., Chicago 1, Ill., has initiated grants-in-aid in hematological research.

Dr. William C. Menninger, F.A.C.P., Governor of the American College of Physicians for Kansas, addressed the 3rd Annual Pacific Northwest Industrial Health Conference at Portland, during September, on "Mental Health Problems in Industry." Dr. Menninger also moderated a panel discussion in which the viewpoints of management, the industrial physician, the industrial nurse, and the plant worker were presented.

Dr. W. Edward Chamberlain, F.A.C.P., of Philadelphia, has been installed as President of the American Roentgen Ray Society. His inaugural address, "Benefits to Mankind Through Integration of Physiology and Radiology," was given at that Society's 57th Annual Meeting at Los Angeles, September 25–28.

Dr. J. Lamar Callaway, F.A.C.P., Durham, N. C., was recently elected Secretary of the American Dermatological Association.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, and Dr. Franz K. Bauer, (Associate), Los Angeles, were elected Vice President and Vice President-Elect, respectively, of the Society of Nuclear Medicine, recently.

Dr. Dwight L. Wilbur, Regent, San Francisco, officially represented the President and Officers of the American College of Physicians at the Forty-second Annual Clinical Congress of the American College of Surgeons at San Francisco, October 8–12, 1956.

FOUNDATIONS' FUND FOR RESEARCH IN PSYCHIATRY

The number of highly qualified scientists engaged in mental health research is relatively small despite the widespread recognition of the importance of such research. Psychiatrists are, for the most part, involved in clinical practice, and their professional training does not usually provide them with the specialized skills needed for research. Biologists and social scientists doing research in the area of mental health are often unfamiliar with clinical problems. The need for comprehensive research training in this field is said to remain acute. In order to assist in the development of highly qualified investigators in the mental health field, the Ford Foundation, on January 12, 1956, awarded a grant of \$3,682,000 to the Foundations' Fund for Re-

search in Psychiatry. This sum is to be expended or committed during a period of five years,

The Program supported by this grant consists of three parts: (1) advanced fellowships; (2) summer stipends for medical students; and (3) funds for staff appointments.

Further details about these fellowships may be obtained by inquiry to the Foundations' Fund for Research in Psychiatry, 251 Edwards St., New Haven 11, Conn.

"MEDICAL HORIZONS"

"Medical Horizons" is the title of a series of television broadcasts organized and conducted by Ciba Pharmaceutical Products, Inc., Summit, N. J. Among the Fellows of the College who have participated prominently in these programs are Dr. Nathan Kline, F.A.C.P., Rockland State Hospital, Orangeburg, N. Y., (Sept. 30); Dr. Howard Rusk, F.A.C.P., Institute for Mental and Physical Rehabilitation, New York, N. Y., (Oct. 7); Rear Admiral Bartholomew W. Hogan, F.A.C.P., Surgeon General of the U. S. Navy, (Oct. 14). The programs are scheduled each Sunday afternoon at 4:30 p.m. (EST).

"FIRST A PHYSICIAN"

"First A Physician," a dramatic motion picture portraying the rôle of the radiologist on the medical team, had its premiere showing at the annual meeting of the Roentgen Ray Society at Los Angeles in September. The film was produced by the Du Pont Company in coöperation with the American College of Radiology. It depicts facets of diagnostic and therapeutic radiology in the finding and treatment of various human ailments and diseases, including cancer. In the non-technical 27-minute color film are, in addition to the radiologist, these members of the medical team: family physician, surgeon, intern, nurse, psychiatrist, x-ray technician, and anesthesiologist. The film is now available in 16 mm prints for showing to medical, civic, school, and other interested groups throughout the country. Applications should be made to the Du Pont Public Relations Dept., Wilmington 98, Del.

Dr. Theodore G. Klumpp, F.A.C.P., President of Winthrop Laboratories, was recently awarded an honorary membership in the American Hospital Association. The citation, in part, read: "for outstanding contributions made to the health field through exemplary, selfless service to various commissions, committees and organizations . . . (and) your service on the Commission on Chronic Illness and the inspired leadership you gave to the Medical Services Task Force of the Hoover Commission."

Dr. Perk Lee Davis, F.A.C.P., Paoli, Pa., took part in a Symposium on Diseases of the Chest at the Mayo Clinic Reunion from September 26 to 29.

Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., was installed as President of the American Heart Association at its meeting in Cincinnati, Ohio, October 26-November 2, 1956. Dr. Allen succeeded Dr. Irvine H. Page, F.A.C.P., of Cleveland, who will become Chairman of the Scientific Council. Among the medical and scientific leaders appearing on the program, almost without exception, they were members of the American College of Physicians.

CLEVELAND HEALTH MUSEUM

The Cleveland Health Museum is dedicated to the purpose of promoting better health through the development of exhibits, models, slides, and other instrumentalities of visual means. "How to Make Health Visible" is the title of its catalogue "of effective tools for promoting better health." The Cleveland Health Museum Workshop is a pioneer and leader in the creative field of exhibits. Among its notable advances has been perfection of plastic processes which give modern exhibition a "new look." Exhibits have been already developed in six categories: Section I—Human Biology; Section II—Dickinson-Belskie Collection; Section III—Growth and Development; Section IV—Nutrition; Section V—School Health; Section VI—Medicine and Public Health.

The catalogue carries a listing, description, and in many cases illustrations of the exhibits that have already been prepared. Many of these exhibits are available for loan. Furthermore, there is an extensive health film library available for viewing or for loan to group meetings. The Museum, also, has made a series of slides available both for loan and for duplication, except where otherwise noted.

The catalogue is available, \$1.00 per copy. The address of the Museum is 8911 Euclid Ave., Cleveland 6, Ohio.

LESTER TAYLOR MEMORIAL SCHOLARSHIP

A \$500 scholarship, named for the Cleveland Health Museum's first president, has been made available by the Women's Committee of the Museum to any qualified graduate student interested in: (1) school health education; (2) visual methods in health education; (3) educational work in museums.

Special projects, tailored to the interests and requirements of the candidate, are set up for completion in from one to three months. All projects must be completed on the Museum premises under the direction and supervision of its professional staff, and a written report of the project is required.

A tuition fee of \$100 will be paid to the Museum from the \$500 stipend. The remainder is paid directly to the candidate for living and other expenses.

Requests for applications may be sent to Bruno Gebhard, M.D., Director, Cleveland Health Museum, 8911 Euclid Ave., Cleveland 6, Ohio.

U. S. Atomic Energy Commission Offers Special Fellowships in Industrial Medicine

The Atomic Energy Commission offers fellowships which provide advanced training and on-the-job experience in the field of Industrial Medicine, particularly in relation to the atomic energy industry. The selection of Fellows is made by the Atomic Energy Commission on recommendation of the Committee on A.E.C. Fellowships in Industrial Medicine. For the academic year 1957–1958, eight Fellowships will be available.

The Fellowships are open to men and women physicians who are citizens of the United States, who have graduated from an approved medical school at least two years prior to beginning tenure of the Fellowship and who are licensed to practice medicine in one of the states or territories of the United States. Successful candidates will be required to have a full F.B.I. background investigation and to be cleared by the Commission prior to award of a Fellowship.

The stipend during a Fellowship or academic year is \$3600. This is usually divided into a minimum of 9 or a maximum of 12 equal payments, depending upon the

starting date elected by the Fellow. Certain additional amounts are allowed for candidates who are married, and for dependent children.

The Fellowship year of academic training may be taken at a university offering an approved graduate course in Industrial Medicine which can provide special training facilities in the health problems associated with the Atomic Energy Program.

Applications for the academic year 1957-1958 should be filed before January 1, 1957. Inquiries should be addressed to A.E.C. Fellowships in Industrial Medicine, Atomic Energy Project, University of Rochester School of Medicine and Dentistry, Rochester 20, N. Y., Attention of Dr. Henry A. Blair.

ARMED FORCES MEDICAL LIBRARY TRANSFERRED

The Armed Forces Medical Library was transferred on October 1, 1956, to the Public Health Service, Department of Health, Education, and Welfare.

The Armed Forces Medical Library was founded in 1836 as the Library of the Surgeon General's Office, U. S. Army. Today it is one of the largest and most important medical libraries in the world. It contains almost a million volumes, representing literature on medicine, dentistry, pharmacy, and allied sciences in all languages and of all times. Its books are loaned to other libraries throughout the

In administering the National Library of Medicine, the Surgeon General of the Public Health Service will be assisted by a Board of Regents consisting of ten persons to be appointed by the President and confirmed by the Senate. Ex officio members of the Board will be the Surgeons General of the Public Health Service, the Army, Navy, and Air Force, the Chief Medical Director of the Department of Medicine and Surgery of the Veterans' Administration, the Assistant Director for Biological and Medical Sciences of the National Science Foundation, and the Librarian of Congress.

The National Library of Medicine Act also authorizes the construction of adequate facilities to house the Library on a site to be selected by the Surgeon General of the Public Health Service at the direction of the Board of Regents.

DERMATOLOGIC RESEARCH AND TEACHING FELLOWSHIPS

A number of dermatologic research and teaching fellowships have been made available at the New York Skin and Cancer Unit of the New York University-Bellevue Medical Center, it has been announced by Dr. Marion B. Sulzberger, F.A.C.P., Director of the service.

These fellowships are available on two levels. One is for dermatologists who have completed their three-year, full-time training in dermatology and who are desirous of embarking on or continuing in a research or teaching career in special fields of dermatology—immunology, mycology, oncology, physiology, radiation (including radioactive isotopes). This fellowship pays a stipend of \$7,000 a year.

The second type of fellowship, at \$5,000 annually, is available to graduate students or residents who have completed their basic science year at a recognized institution and who plan to do research or to assist in teaching in special fields.

tution and who plan to do research or to assist in teaching in special fields.

Applicants should apply to the Director, Service of Dermatology, New York Skin and Cancer Unit, 330 Second Ave., New York 3, N. Y.

Maj. Gen. Paul I. Robinson, F.A.C.P., has been appointed Executive Director of the new dependents' civilian medical care program, according to the Army Surgeon General. He will head a program established to implement a bill enacted by Congress on June 7 providing for medical care in civilian facilities to dependents of active duty military personnel of the "uniformed services." He will be particularly con-

cerned with the arrangement for medical care received from civilian sources for the wives and children of those in the Army, Navy, Air Force, Public Health Service, Coast and Geodetic Survey, and the Coast Guard. Approximately 800,000 persons in this category have not received medical care previously because they have not resided near military medical facilities.

UNIVERSITY OF PENNSYLVANIA'S NEW DONNER CENTER FOR RADIOLOGY

The University of Pennsylvania has broken ground for the construction of its new William H. Donner Center for Radiology, and expects to complete this structure by late 1957 or early 1958.

The Center will bear the name of the late William H. Donner, Pennsylvania industrialist and philanthropist, in recognition of his long interest in radiological diagnosis and treatment. The Donner Foundation, which he founded, has made a grant of \$750,000 to the University to establish this radiology center.

Physicians, chemists, and physicists will carry on cooperative research projects in the new Center. These will be in the fields of radioactive isotopes, high energy radiation, and similar projects with special significance in the field of medical sciences.

The new Center will consist of three floors, providing 16,000 square feet of floor space, and will be connected with the present Department of Radiology of the University Hospital.

At a ceremony at the Cuban Embassy in Washington in September, Dr. Miguel Angel Campa, Cuban Ambassador, conferred upon Lt. Col. William H. Crosby (Associate), Chief of the Department of Hematology, Walter Reed Army Institute of Research, the decoration of the National Order of Merit "Carlos J. Finlay."

The Finlay Order of Merit was created in 1928 to honor those Cuban citizens or foreigners who made exceptional contributions to public health in the Republic of Cuba. It was named after Carlos J. Finlay, the Cuban doctor who collaborated with Maj. Walter Reed in discovering the rôle of the mosquito in yellow fever.

Col. Crosby is Chief of the Walter Reed Hematology Department and previously served as Medical Specialist, Queen Alexandra Military Hospital, London, England. He holds the Bronze Star Medal with two Oak Leaf Clusters. He is the second American Medical Corps Officer to be made a member of the Finlay National Order.

BORDEN AWARD IN NUTRITION

The American Institute of Nutrition is inviting nominations for the 1957 award and gold medal made available by the Borden Company Foundation. The award is given in recognition of distinctive research by investigators in the United States and Canada in which have been emphasized the nutritive significance of the components of milk or of dairy products. The award will be made primarily for the publication of specific papers during 1956, but the award may be given for important contributions made over a more extended period of time. For details, consult Cosmo G. Mackenzie, Sc.D., Department of Biochemistry, University of Colorado School of Medicine, 4200 E. Ninth Ave., Denver 7, Colo.

AWARDS IN DERMATOLOGY

The American Dermato'ogical Association is offering a series of awards for original work related to some fundamental aspect of dermatology or syphilology. The awards consist of four, in amounts of \$500, \$400, \$300, and \$200. For infor-

mation consult Dr. J. Lamar Callaway, Secretary, American Dermatological Association, Duke Hospital, Durham, N. C.

Dr. John D. Hallahan, (Associate), has been promoted to Associate in Internal Medicine at Temple University School of Medicine, Philadelphia. Dr. Jacob Zatuchni, F.A.C.P., was promoted to Assistant Professor of Internal Medicine.

The College of General Practitioners of Great Britain has received a large gift of money to build a new headquarters in London to serve its 3,660 members and associates in Great Britain and overseas. At present, the college has its offices in Chelsea and holds its meetings in the hall of the Society of Apothecaries. The new site will be adjacent to the Royal College of Surgeons.

Dr. Stewart G. Wolf, F.A.C.P., Oklahoma City, and Dr. Eugene A. Stead, Jr., F.A.C.P., Durham, N. C., addressed the 8th Annual Meeting and Scientific Sessions of the Georgia Heart Association at Savannah, Sept. 14–15, their subjects being, respectively, Preliminary Study of Lipoproteins and Life Adjustment in Coronary Occlusion; Personality and Hypertension, and The Autonomic Nervous System and the Circulation.

Dr. Harold Brandaleone, F.A.C.P., Assistant Clinical Professor of Medicine at the New York College of Medicine, was recently elected Treasurer of the Alumni Federation of New York University. In 1954–55 he served as its President. Dr. Brandaleone is also President of the New York State Society of Industrial Medicine, and Medical Director of the Third Avenue Transit System.

Dr. Irving S. Wright, F.A.C.P., College Governor for Eastern New York, addressed the XIV Congress of Internal Medicine of the Soviet Union at Moscow during October.

Dr. William B. Bean, M.D., F.A.C.P., Professor and Head of the Department of Internal Medicine, State University of Iowa College of Medicine, was a visiting lecturer at the University of Miami College of Medicine, Miami, Florida, during the week of September 16–21, 1956.

Dr. Lewis E. January, F.A.C.P., Professor of Medicine at State University of Iowa College of Medicine, has received a grant of \$6,000.00 from the American Heart Association for continuation of the cardiac in agriculture demonstration in Washington County, Iowa.

Dr. Henry Clagett, Jr., F.A.C.P., Wilmington, Delaware, has been made Editor of the Delaware State Medical Journal.

The Twenty-Fourth Annual Assembly of the Omaha Mid-West Clinical Society was held at Omaha, October 29-November 1, 1956. Among the guest speakers and their subjects were the following: Dr. George C. Griffith, F.A.C.P., Los Angeles, Anticoagulants in Cardiovascular Disease—The Differential Diagnosis of Chest Pain

—The Management of Congestive Failure—The Management of Cardiac Arrhythmias; Dr. Chester S. Keefer, F.A.C.P., Boston, Medical Problems in People Over Sixty-Five Years of Age—Complications of Antibiotic Therapy—Chronic Pyelonephritis, Its Natural History and Course—Anti-Infective Therapy, Current Problems.

Dr. C. Wilmer Wirts, M.D., F.A.C.P., Associate Professor of Medicine, Jefferson Medical College, has been appointed Director of the Postgraduate Institute of the Philadelphia County Medical Society.

At the election of officers of the California Society of Internal Medicine, September 29, 1956, Dr. William C. Mumler, (Associate), Los Angeles, was elected President, and Dr. Robert L. Smith, Jr., F.A.C.P., of San Francisco, was elected Vice President.

Dr. Thurman K. Hill, (Associate), Santa Barbara; Dr. Walter P. Martin, F.A.C.P., Long Beach; Dr. Paul V. Morton, (Associate), San Jose; Dr. James H. Thompson, F.A.C.P., San Francisco, were reëlected to the Council for another year.

New members on the Council are Dr. Edward Shapiro, (Associate), Beverly Hills; and Dr. Joseph F. Sadusk, Jr., F.A.C.P., Oakland.

Dr. David B. Carmichael, M.D., (Associate), has been appointed Director of The Heart Center in Sharp Memorial Community Hospital.

Dr. F. A. L. Mathewson, F.A.C.P., was elected president of the Canadian Heart Association, at its annual meeting in Quebec city in June 1956. Dr. Mathewson is also director of the Canadian Heart Foundation.

Dr. Thomas M. Rivers of New York City, formerly Vice President of the Rockefeller Institute for Medical Research, has been appointed Medical Director of the National Foundation for Infantile Paralysis, it has been announced by Mr. Basil O'Connor, President of the March of Dimes organization. Dr. Rivers took over his new post on November 1, and succeeds Dr. Hart E. Van Riper.

Initial grants totalling \$765,159 to assist in the construction of medical research facilities were announced in October by Dr. Leroy E. Burney, F.A.C.P., Surgeon General of the Public Health Service, Department of Health, Education, and Welfare. These are the first Federal grants under a 3-year, \$90-million program enacted by the recent Congress to aid public and private institutions in building more and better research facilities. Dr. Burney's approval of the grants was based on the recommendation of the newly created National Advisory Council on Health Research Facilities. Grants must be matched on a 50-50 basis by the institutions.

Among the institutions named in this first award were: Massachusetts General Hospital, Albany Medical College, Christ Hospital Institute of Medical Research of Cincinnati, University of Pennsylvania, University of Minnesota Medical School, University of Minnesota College of Medical Sciences, and Georgetown University.

The U. S. Department of Health, Education, and Welfare has announced the appointment of a government advisory committee to study and develop methods of adapting hospital facilities and services more closely to the varying needs of patients.

The objective will be to help hospitals in their efforts to improve care, and to reduce costs particularly for patients who need only limited services. Dr. Russell A. Nelson, F.A.C.P., Director of Johns Hopkins Hospital, Baltimore, Md., has been appointed Chairman, and the Committee has been officially named "The Advisory Committee on Hospital Facilities and Services." The Committee will work closely with Dr. Lowell T. Coggeshall, F.A.C.P., Special Assistant to Secretary Marion B. Folsom for Health and Medical Affairs.

The New York University Post-Graduate Medical School conducted two post-graduate courses during November under the direction of Dr. J. Scott Butterworth, F.A.C.P., in Cardiac Roentgenology and Electrocardiography, respectively.

Numerous other short courses are offered at this institution from time to time, and further information may be obtained from the Dean, New York University Post-Graduate Medical School, 550 First Ave., New York 16, N. Y.

Dr. David I. Abramson, F.A.C.P., Head of the Department of Physical Medicine and Rehabilitation of the University of Illinois, Research and Educational Hospitals, Chicago, is author of a new book on *Diagnosis and Treatment of Peripheral Vascular Disorders*, published in August, 1956, by Paul B. Hoeber, Inc., New York.

Dr. Andrew L. Banyai, F.A.C.P., Milwaukee, Wis., has been awarded the Carlo Forlanini gold medal of the Italian Federation Against Tuberculosis at the IV International Congress on Diseases of the Chest held in Cologne, Germany, during August of 1956. This award was given in recognition of his clinical research work in chest diseases, particularly for the introduction of artificial pneumoperitoneum in the treatment of pulmonary tuberculosis. Dr. Banyai is Associate Clinical Professor of Medicine at Marquette University School of Medicine, and past President of the American College of Chest Physicians.

Dr. William Dock, F.A.C.P., for many years Professor of Medicine at State University of New York, College of Medicine at New York City, joined the Palo Alto Clinic, 300 Homer Ave., Palo Alto, Calif., on October 1, 1956.

Dr. Edmond K. Doak, F.A.C.P., has been reappointed Governor for the State of Texas for the American Diabetes Association.

Dr. Nathaniel E. Reich, F.A.C.P., gave an address on August 14, 1956, before the faculty and members of the Research Institute of the Academy of Medical Sciences in Moscow, USSR, prior to his address at the international meeting of the American College of Chest Physicians in Cologne, Germany, on August 22, 1956.

Dr. John S. LaDue, F.A.C.P., of Cornell University Medical School, New York City, delivered an address entitled, "The Management and Care of the Patient with Inoperable and Terminal Cancer," before the annual series of cancer lectures of Northwestern University Medical School at Chicago, on November 21.

Among the distinguished guest speakers at the 34th Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society were the following Fellows of

the College: Dr. W. A. D. Anderson, Miami, Fla., "Tumors of Childhood"; Dr. Laurance W. Kinsell, Oakland, Calif., "Observations Regarding the Clinical and Experimental Use of the Insulin Sparing Sulfonamides"; Dr. Edgar Hull, New Orleans, La., "Emergency Use of Corticoids and Corticotropins"; Dr. Carl V. Moore, St. Louis, Mo., "Thrombocytopenic Purpura, Its Pathogenesis and Treatment."

Dr. Cecil J. Watson, Minneapolis, has been elected President of the Minnesota chapter of the Arthritis and Rheumatism Foundation.

Dr. Thaddeus D. Labecki, F.A.C.P., Jackson, Miss., and Dr. E. Hugh Luckey, F.A.C.P., New York City, addressed the Sixth Annual Scientific Assembly of the Ohio Academy of General Practice, Sept. 19–20. Their respective subjects were: "Trends in Pediatric, Adult, and Geriatric Nutrition" and "Management of Congestive Heart Failure."

The University of Tennessee College of Medicine, Memphis, will offer a short postgraduate course, Selected Problems in Internal Medicine, May 22-24, 1957.

The 4th Annual Tennessee Valley Medical Assembly held at Chattanooga, Tenn., Oct. 1–2, was addressed by the following Fellows of the American College of Physicians: Dr. Walter C. Alvarez, Chicago, New Observations on Little Strokes; Dr. Philip S. Hench, Rochester, Minn., Treatment of Rheumatoid Arthritis; Dr. Eugene P. Pendergrass, Philadelphia, Responsibility of the General Practitioner and the Radiologist in Diagnosis of Curable Cancer of the Lung; Dr. Tom D. Spies, Birmingham, Ala., Recent Advances in Treatment of Nutritional Disorders; Dr. Francis E. Senear, Chicago, Diagnosis and Treatment of the Bullous Dermatoses; Dr. Henry L. Bockus, Philadelphia, Chronic Regional Enteritis; The Acute Abdomen.

Dr. Frank W. Otto, F.A.C.P., Los Angeles, has been appointed Chief Advisor to the Department of Mental Hygiene of the State of California. He proposes to elevate standards of both private and state institutions throughout the State.

Dr. Lester Meister, (Associate), Long Beach, Calif., has been advanced to Associate Clinical Professor of Medicine at the University of California at Los Angeles.

Dr. Stephen Elek, F.A.C.P., Los Angeles, has been promoted to the position of Associate Clinical Professor of Medicine at the University of Southern California.

Dr. Herbert McCoy, (Associate), La Jolla, has been elected to the Board of Directors of the San Diego Heart Association. Dr. McCoy is the Chief of the Medical Service at Scripps Memorial Hospital and Head of the Medical Department of Casa de Manana.

Dr. Wetherbee Fort, F.A.C.P., Baltimore, is Treasurer of the Medical and Chirurgical Faculty of the State of Maryland.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., former Governor of the American College of Physicians, has been elected to membership on the Council on Constitution and By-Laws of the American Medical Association.

Dr. Donald R. Fitch, (Associate), Glendale, Calif., addressed the Annual Meeting of the Academy of General Practice at Los Angeles, Oct. 15, on "Aftercare of the Operated Peptic Ulcer."

Dr. Marion A. Blankenhorn, F.A.C.P., Cincinnati, Ohio, has been appointed Director of Education in the Department of Internal Medicine of the Jewish Hospital in that city. He retired last year as the Taylor Professor of Medicine and Director of the Department of Internal Medicine in the University of Cincinnati College of Medicine, and as Director of the Medical Service at the Cincinnati General Hospital. He was appointed to those posts in 1935, and he remains as Professor Emeritus at the University of Cincinnati College of Medicine.

Dr. Blankenhorn has been in the past the Governor of the American College of Physicians for the State of Ohio, and a member of its Board of Regents. During the past year he has been the Director of the Study of Hospital Standards in Medicine for the College. It is anticipated that in his new position he will still continue

his participation in the work for the American College of Physicians.

A.M.A. PHYSICIANS' PLACEMENT SERVICES

The American Medical Association operates a nation-wide network of state medical society services, including a physicians' placement service, bringing together communities seeking doctors and doctors seeking a place to practice. Although the emphasis remains on the general practitioner and the community, group practice units, industry, government agencies, and even hospitals are making more and more use of these services and, as a result, are bringing the various specialties into the picture. Full details are available through Dr. Willard A. Wright, Chairman, Committee on Medical and Related Facilities, American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.

RESIDENCIES IN PSYCHIATRY AVAILABLE

The Veterans Administration Hospital, Lyons, N. J., has available residencies in Psychiatry for a one to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences, and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers as well as an Annual Institute at the hospital. Training may commence at any time.

At the last annual meeting of the Omaha Mid-West Clinical Society on December 3, 1956, Dr. Donald J. Wilson, F.A.C.P., was elected a member of the Executive Committee. Dr. Edmond M. Walsh, F.A.C.P., College Governor for Nebraska, is also a member of this Committee. Drs. Henry J. Lehnhoff, Jr., F.A.C.P., and John D. Hartigan (Associate), were named co-chairmen of the specialty section of internal medicine.

FELLOWSHIP IN HEMATOLOGY

A one-year appointment (option of renewal) beginning July 1, 1957, is available in the Department of Medicine, University of Maryland School of Medicine. Annual stipend \$3,000 to \$3,500, dependent on marital status. The fellowship offers opportunities for training in clinical hematology as well as investigative work in this field. Inquiries should be addressed to Dr. Milton S. Sacks, F.A.C.P., Professor of Clinical Medicine, University Hospital, Baltimore 1, Md.

Corrections

In the Abstract of Minutes of the Joint Executive Session of the Board of Regents and Board of Governors, published in this journal, Vol. 45, No. 4 (October, 1956), page xciv, reference was made to the report of the Committee on Certification of Non-Medical Personnel, "clinical pathologists" were mentioned in error among certain groups of non-physicians. The Committee's report referred only to non-physician specialists.

In the November issue of the Annals of Internal Medicine, page 104, the current personnel of the Board of Governors of the American College of Physicians was published. The present Governor of the College for the United States Public Health Service is Dr. Leroy E. Burney. Dr. Leonard A. Scheele retired several months ago as the Surgeon General of the Public Health Service and as the College Governor for that Service.

OBITUARIES

DR. ANTON JULIUS CARLSON

Anton J. Carlson, M.A.C.P., formerly professor and chairman of the department of physiology at the University of Chicago, died of cancer, September 2, 1956, in Albert Merritt Billings Hospital.

Dr. Carlson was born in Sweden, January 29, 1875, and came to America in 1891. He received his B.S. degree from Augustana College in 1898 and his Ph.D. degree from Stanford University in 1903. He served as research assistant in physiology at Stanford and then became associated with the Carnegie Institution. In 1904 he joined the faculty of the University of Chicago where, in 1929, he became Frank P. Hixon Distinguished Service Professor.

He was Secretary of the Section on Pathology and Physiology of the American Medical Association from 1912 to 1914. He became Chairman, serving until 1915. In 1946 he was the recipient of the Distinguished Service Medical of the American Medical Association. He received the Distinguished Service Citation of the Minnesota State Medical Association and in 1953 was voted humanist of the year. He was awarded honorary degrees (M.D., LL.D., and Sc.D.) by eight universities and colleges.

He was President of the American Physiological Society, the Institute of Medicine of Chicago, American Association of University Professors, Federation of American Societies for Experimental Biology, American Association for the Advancement of Science, National Society for Medical Research, Research Council on Problems of Alcohol, and the Chicago Committee on Alcoholism.

During World War I he was assigned to the Sanitary Corps as a Lieutenant Colonel in the United States Army and worked with the American Relief Expedition in Europe.

Dr. Carlson became a Fellow of the American College of Physicians in 1926, and was elected a Master of the College in 1947. He contributed frequently to the literature of experimental physiology and was the author of several books.

Dr. Carlson was one of the giants of modern physiology. He trained hundreds of medical students in physiology as well as specialists in physiology who are now chairmen of physiology departments in various schools throughout the United States. Many of his students for advanced degrees in physiology have become distinguished physicians.

He was always fearless and outspoken. He was aware of how little we really know and had no use for sham and pretense. Pretense was a deadly sin with him. While he was fearless and outspoken, his conversation was usually spiced with quick humor.

To his students he was always referred to as "Ajax," and his favorite question, "Vat is de effidence?".

Carlson is dead, but his attitude and spirit will live forever in those whom he taught, stimulated and inspired. He is survived by his widow, Esther, who lives at 5228 S. Greenwood Ave., Chicago 15, Ill.

HOWARD WAKEPIELD, M.D., F.A.C.P., Governor for Northern Illinois, A.C.P.

DR. HARRY A. ALEXANDER

Dr. Harry A. Alexander, F.A.C.P., was born in Indianapolis, Ind., August 29, 1899, and died in Boulder, Colo., April 15, 1956. He was educated at Butler College and the University of Indiana, receiving both Bachelor of Science and Doctor of Medicine degrees. He was a member of Sigma Chi and Phi Rho Sigma fraternities.

He interned in the Indiana City Hospital, 1926–1927, and then engaged in private practice in Indiana. He later moved to Boulder, Colo., to be associated with Dr.

O. M. Gilbert, but in 1932 began his own private practice.

Dr. Alexander was a member of the Boulder County and Colorado Medical Associations, and the American Medical Association. He became a Fellow of the American College of Physicians in 1944. He was active in the Congregational Church, having served it as moderator. His hobby was the cultivation of roses, for

which he received more than state-wide recognition.

Dr. Alexander had distinguished service with the Army Medical Corps in World War II, having been commissioned a major. His assignments included posts in England, France and Germany. He returned to the States in July, 1945 on a 30-day leave after 18 months overseas service. He was then detached from a China-Burma-India Hospital Group just 24 hours before it was to leave an European port. His next assignment was service in the South Pacific, but the end of the war caused him to be assigned to service in the U. S. until November, 1945, when he was placed on terminal leave.

Besides his wife, Rebecca, a daughter and two sons survive.

LAWRENCE W. HOLDEN, M.D., F.A.C.P.

DR. GEORGE ERICK BELL, SR.

George Erick Bell, Sr., M.D., F.A.C.P., of Wilson, N. C., died unexpectedly of a heart attack on May 26, 1956, at Morehead City, N. C. He was born April 7, 1893, the son of a physician of Wakefield, Wake County, N. C., and was a graduate of Wake Forest College (1919) and Jefferson Medical College of Philadelphia (1921), after military service as a hospital apprentice in the U. S. Navy. After internship in Philadelphia he entered the general practice of medicine in Wilson in 1922. In 1931, he joined the staff of Woodard-Herring Hospital, with special interest in Pediatrics. From 1949 to 1951 he was President of the Staff.

His many medical and civic interests included the Wilson County Medical Society (President, 1925), Wilson County Board of Health (1928–47), Medical Director, Sudan Temple (Shrine, 1933–47, Potentate, 1948), Seaboard Medical Society (President, 1942), the North Carolina State Medical Society, and the Southern Medical and American Medical Associations. He was elected to Fellowship in the

American College of Physicians in 1939.

Dr. Bell served as a Trustee of the Eastern North Carolina Sanatorium after being Chairman of the Building Committee, and was a Trustee of Wake Forest College. In 1955, he was named "General Practitioner of the Year" by the North

Carolina Medical Society.

Survivors include Mrs. Bell, the former Inza Tomlinson, and two daughters, Mrs. Hubert Walston and Joanne Bell (1501 West Nash St., Wilson, N. C.), and Dr. George Erick Bell, Jr., Resident in Orthopedic Surgery, Duke Hospital, Durham, N. C.

ELBERT L. PERSONS, M.D., F.A.C.P., Governor for North Carolina, A.C.P.

DR. WILLIAM MORGAN BRACE

Dr. William Morgan Brace, a Fellow of the American College of Physicians since 1931, died on April 23, 1956, aged 62, of fibrosis of the lungs and cor pulmonale.

Dr. Brace was born at Detroit, Michigan, June 12, 1894. He received his A.B. degree in 1918 and his M.D. degree in 1923, from the University of Michigan. His Junior Internship was spent at the Maryland General Hospital in Baltimore; his Senior Internship at the University of Michigan Hospital, the latter extending over four years. He had served on the faculty of the University of Michigan Medical School in various capacities—Instructor in Public Health and Hygiene, Senior Medical Adviser, Assistant Professor of Public Health and Hygiene. He had served respectively as Secretary, Treasurer and President of the Washtenaw County Medical Society; he was a member of the Michigan State Medical Association and a Fellow of the American Medical Association. His early publications appeared in such well-known journals as the Annals of Internal Medicine.

DR. WALTER PAUL DAVENPORT

Dr. Walter Paul Davenport, F.A.C.P., died in Minneapolis, Minnesota, on July 17, 1956. He was a graduate of the University of Illinois College of Medicine and of the Army Medical School, Washington, D. C. He was a member of the Medical Department of the United States Army from 1913 to 1945, retiring as a Colonel.

Dr. Davenport had a long and distinguished career. He was Director of Medical Relief in the Near East in 1919 and 1920. He was Associate Director of Medical Relief of the American Relief Administration during the Russian famine in 1921 to 1924. He was a member of General Eisenhower's staff at Supreme Headquarters in World War II and was Chief Surgeon in the Antilles Department, United States Army, 1940–1943. In this latter capacity as the Department Surgeon he was responsible for the great expansion of personnel that took place during this time. He was a member of the American Medical Association and a Fellow in The American College of Physicians (1943). He is survived by his widow, Mrs. Lillian (Leedstrom) Davenport and two daughters, Mary L. and Jane A.

WESLEY W. SPINK, M.D., F.A.C.P., Governor for Minnesota

DR. HARRY ARNOLD DURKIN

Dr. Harry Anthony Durkin, F.A.C.P., was born on November 13, 1890, in Peoria, Illinois. He received his B.A. degree in 1911 from Holy Cross University and his M.D. degree from Harvard University in 1915. He was made a member of Alpha Omega Alpha. He interned and took postgraduate training in internal medicine at Massachusetts General Hospital, following which he entered the Army in World War I, and served as a lieutenant in the Medical Corps, 1917–18. Dr. Durkin was prominent in medical affairs at Peoria and was in great demand as a consultant and as a speaker before medical groups. He was a member of the attending staff of St. Francis Hospital, Peoria, from 1919 to the time of his death; consulting physician, Peoria Municipal Tuberculosis Sanitarium; member, Illinois Advisory Council for Pneumonia Control Program; member of the Board of Health, City of Peoria. In addition to the Local, State, and National (A.M.A.) societies, Dr. Durkin was a member of the American Heart Association and the Illinois Heart Association (President, 1944). He was certified by the American Board of Internal Medicine

in 1937 and he became a Fellow of the American College of Physicians in 1938. He had been in ill health for some time before death which occurred on May 20, 1956, at Peoria. He is survived by his wife, Mrs. Rose M. Durkin, 101 Roanoke Avenue, Peoria, Illinois, to whom we all extend our sympathy.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P., Governor for Southern Illinois

DR. HARRY JAY EPSTEIN

We record with regret the death of Dr. Harry Jay Epstein, F.A.C.P., on July 9, 1956. Dr. Epstein was born in New York City on December 25, 1903. Before becoming a physician, he received the degree of Ph.G. from the Philadelphia College of Pharmacy and Science in 1923. Wishing to become a practicing physician some years later, he obtained his M.D. degree from Temple University School of Medicine. Following his graduation from Temple University in 1931, he received additional training at the University of Chicago (Billings Hospital) and at the New York University Postgraduate School.

Dr. Epstein taught actively in Hahnemann Medical College and Hospital from 1948 until his death. He held the title of Instructor in Medicine from 1948 to 1951, Associate in Medicine, 1951 to 1954, and Assistant Professor of Medicine from 1954 until his death in 1956. He served the Albert Einstein Medical Center, Southern Division, long and faithfully, having the title of Adjunct Physician from 1935 to 1953, when this institution was known as the Mt. Sinai Hospital, and having the title of Associate Attending Physician from 1953 to 1956. In addition to membership in his County and State Medical Societies, he belonged to the American Medical Association and American Society of Parasitologists. In 1955, he became a Fellow of the American College of Physicians.

To Dr. Epstein's wife, Mrs. Pearl G. Epstein, 5217 Lebanon Avenue, Philadelphia, the College extends its deep sympathy.

THOMAS M. McMillan, M.D., F.A.C.P., Governor for Eastern Pennsylvania, A.C.P.

DR. JOHN EUGENE GONCE, JR.

Dr. John Eugene Gonce, Jr., F.A.C.P., Madison, Wis., was born at Elkton, Md., Oct. 17, 1893, and died March 25, 1956, at Madison, Wis. Dr. Gonce held his A.B. degree from the University of Delaware (1913), and his M.D. degree from the University of Pennsylvania School of Medicine (1918). He pursued postgraduate training at Children's Hospital of Philadelphia, and at the Harriet Lane Home in Baltimore. His chief interest was in the field of pediatrics.

Dr. Gonce served as Clinical Instructor in Medicine at the University of Wisconsin Medical School beginning in 1919, and rose to Professor of Pediatrics at that institution in 1932, a post which he held until his death. He had been Associate Pediatrician at the State of Wisconsin General Hospital since 1925.

He was a member of the Dane County Medical Society, Wisconsin State Medical Society, American Medical Association, Chicago Pediatrics Society, and some others. He was a Diplomate of the American Board of Pediatrics, and had been a Fellow of the American College of Physicians since 1929.

The record discloses that he wrote extensively in the field of pediatrics, and he contributed many articles to leading medical journals.

His death was due to acute coronary occlusion. He is survived by his widow, Mrs. Louise Allyn Gonce, 2221 Chamberlain Ave., Madison 5, Wis.

DR. WALTER HENRY KROMBEIN

Dr. Walter Henry Krombein, F.A.C.P., of Buffalo, New York, died July 24, 1956, after an illness of three days. He was born in Buffalo, New York, September 17, 1900, and received his academic education at the University of Buffalo, receiving his M.D. degree in 1924. He then interned in Buffalo General Hospital, and served his last year as Resident Physician. Dr. Krombein was then appointed Assistant in Medicine, 1925–29, Instructor in Medicine, 1929–1930, Associate in Medicine, 1930–37, and Assistant Professor of Medicine, 1937–1956, at the University of Buffalo School of Medicine. For several years he conducted a course in physical diagnosis at the University. In addition to his teaching responsibilities, he was Assistant Physician at Buffalo General Hospital, 1936–56; Consultant in Internal Medicine United States Marine Hospital No. 3, 1933–56; Clinical Assistant in Medicine, Buffalo City Hospital, 1928–56; Physician to Training School, Children's Hospital, 1938–56; and Clinical Assistant in Medicine, Meyer Memorial Hospital, 1928–56.

Dr. Krombein was a member of the Erie County Clinical Society, New York State Medical Society, American Medical Association, Omega Upsilon Phi, Phi Chi, Alpha Omega Alpha, Buffalo Academy of Medicine, Diplomate of the American Board of Internal Medicine, and a Fellow (1937), of the American College of Physicians.

Dr. Krombein was active in the Erie County Medical Society, and served as a member of the Bulletin Publication Committee for more than 25 years. He also served on the Workmens Compensation Committee for several years and on other committees at various times. For several years, he acted as a Consultant in Internal Medicine in the United States Public Health Service.

Dr. Krombein lived at home with his mother and never was married. His passing in the prime of his professional productivity leaves a void in the medical school, the hospital, his office, and most of all in his mother's heart.

JOHN H. TALBOTT, M.D., F.A.C.P., Governor for Western New York, A.C.P.

DR. EUGENE MABLEY LATH

Dr. Eugene Mabley Lath, (Associate), of Rochester, New York, died in Rochester on May 16, 1956. He graduated from the University of Buffalo School of Medicine, 1907, and practiced in Rochester throughout his professional career. His hospital appointments included: Medical Examiner for the United States Marine Corps, 1929 to 1935; Physician and Member of the Board of Directors of Park Avenue Hospital and Associate Physician at St. Mary's Hospital, all in Rochester. He was a member of the American Medical Association, the New York State Medical Society, the Monroe County Medical Society, the American Academy of Medicine, Rochester Medical Association, New York Pathological Society, and Nu Sigma Nu Medical Fraternity.

There are no immediate relatives. Dr. Lath was a charter member of the American Congress on Internal Medicine (1916); when it was merged with the American

can College of Physicians in 1926, he became an Associate of the College, with the privilege of retaining that status indefinitely, which he elected to do. He was a general practitioner throughout his professional career and although a member of several medical societies, as noted above, he was not an active participant in scientific meetings. In his professional work, however, he endeavored to reflect progressive thought of the times; he was of a reserved nature and a deeply religious man.

JOHN H. TALBOTT, M.D., F.A.C.P., Governor for Western New York, A.C.P.

DR JAMES WARREN LAWS

Dr. James Warren Laws, F.A.C.P., died on June 15, 1956 at his home in El Paso, Texas, where he had been a resident for 39 years. He was born October 12, 1873, at Bethlehem, Mississippi, was a graduate of the Arkansas State Normal College in 1893, and received his M.D. degree from the Memphis Hospital Medical College, Memphis, Tennessee in 1898. Dr. Laws served an internship of one year there, and served two years as an intern and Acting Surgeon with the United States Public Health Service and Marine Hospital in Memphis. He then became the Acting Assistant Surgeon with the United States Marine Hospital and Public Health Service Sanatorium at Fort Stanton, New Mexico, in 1901. Dr. Laws then established the Ranch Sanatorium at Lincoln, New Mexico and was its Director until 1917. From 1918 until 1941 he owned and directed the Hendricks-Laws Sanatorium for the Treatment of Tuberculosis in El Paso, Texas. He was Director of the El Paso Tuberculosis Control Unit, and was in charge of the Tuberculosis Department of the City-County Hospital from 1938 until 1951.

He was a member of the El Paso County Medical Society (President, 1931); Texas Medical Association; American Medical Association; Texas Trudeau Society; National Tuberculosis Association; International Union Against Tuberculosis; and in 1930 became a Fellow, of the American College of Physicians.

Dr. Laws is survived by his wife, Mrs. Grace Gertrude Laws, who resides at 701 N. St. Vrain St., El Paso, Texas.

DAVID W. CARTER, JR., M.D., F.A.C.P., Governor for Texas, A.C.P.

DR. JOHN OWSLEY MANIER

Dr. Owsley Manier died at his home in Nashville, Tennessee, September 1, 1956, from a cerebral thrombosis which occurred in 1953.

He was born in Nashville on March 18, 1887, where he attended public school and the Wallace University School before entering Vanderbilt University.

At an early age he was regarded as an excellent student, a reputation which he never lost, but he first gained National recognition in Vanderbilt as an all-American half-back in football, earning his letter in football in 1904–05–06.

In Fred Russell's book: "Fifty years of Football at Vanderbilt," many references are made to Dr. Manier's outstanding ability in this game. It was 1906 that marked the first time one of the best teams in the nation agreed to go south to play. This was the game between the Carlisle Indians and Vanderbilt. The under-dogs, Vanderbilt won! In Russell's book he refers to this game and gives a lot of credit to Dr. Manier. To quote: "He (Manier) bucked the line as though it were made of tissue paper."

Dr. Manier received his B.A. from Vanderbilt in 1907, then went to the University of Pennsylvania to study medicine where he not only graduated with honors in 1911, but also was elected to the honorary Medical Fraternity of Alpha Omega Alpha. Dr. T. Grier Miller was one of his classmates.

After a well-rounded interneship in the University of Pennsylvania Hospital he returned to Nashville to specialize in Internal Medicine.

As a teacher of Medicine in Vanderbilt, Dr. Manier was an assistant in Medicine from 1913 to 1924; Assistant Professor of Clinical Medicine, 1924 to 1930; Associate Professor of Medicine, 1930 to 1953.

During all these years he enjoyed an excellent private practice. One of his patients said, "He was always kind, sincere and apparently never in a hurry."

When the American Board of Internal Medicine was founded, he was one of its first members. He became a Fellow in the American College of Physicians in 1926 and three years later, the College Governor for Tennessee, holding that office until 1941. He was selected to serve on the Credentials Committee 1939–41 and 1952–54. Dr. Manier was again honored by being made a Regent of the College in 1951 holding this position until his illness prevented him from doing so in 1954. He exerted a profound influence on every activity of the College with which he was associated and was respected and beloved by every Fellow who knew him.

We can hit only the high spots in reviewing the many accomplishments of Dr. Manier. He served with the Vanderbilt Hospital Unit in World War I. He became president of the Nashville Academy of Medicine in 1928 and President of the Tennessee State Medical Association in 1934. All the important committees he served on in the state are too many to even list.

Dr. Manier had a tremendous influence for good over the entire Medical Profession of Tennessee for a period exceeding twenty-five years. His unusual ability as a leader was recognized all over the state. Whenever the State Organization got into great difficulty, when no one knew what to do (and there were many of those times), he was called upon to straighten us out.

His comprehensive understanding of the problems of medicine are disclosed in a clear manner in his address as State President of Tennessee in 1935. It was entitled: "Some Observations Concerning the Problems of Medicine in Tennessee" (Tennessee State Journal, Volume 28, Number 4). What he said then is almost as valuable now in meeting the problems in any State Medical Organization. In the first part of his speech he said: "No longer can organized medicine, with safety, hold itself behind the screen of science, but rather it must admit it has a political function to perform,—a properly planned attitude to political issues which may affect us in the practice of our profession, our relation with our patients and even our very economic existence."

It is generally agreed that Dr. Manier, by his clear analytical mind, by his fairness, by his wholly unselfish attitude, has contributed more to the real progress of Medicine in Tennessee than any other physician. Anyone who really knew him can understand how the spirit of such a man will go on doing good even though he is no longer with us.

Dr. Manier is survived by his wife, the former Miss Helen Dayton of Morristown, New Jersey, whom he married in 1915, their two sons, Ogden Dayton and Will R. Manier III of Nashville, a sister Mrs. William P. Cooper, Nashville, a brother, Miller Manier, Nashville and seven grandchildren.

WILLIAM CALVERT CHANEY, M.D., F.A.C.P., Memphis, Tenn.

DR. AMADEO VICENTE-MASTELLARI

Dr. Amadeo Vicente-Mastellari, F.A.C.P., Governor of the American College of Physicians for Panama and the Canal Zone, died September 9, 1956, of uremia,

secondary to malignant nephrosclerosis, and malignant hypertension.

Dr. Mastellari became a Fellow of the American College of Physicians in 1941 and a Life Member in 1947. He was born in Panama in 1907. He attended La Salle College, Panama, receiving his B.S. Degree in 1925. He received his Medical Degree in 1931 from George Washington University School of Medicine, Washington, D. C. He interned at the Gorgas Hospital in Ancon and he pursued postgraduate work at the Trudeau School of Tuberculosis and the Henry Phipps Institute of Philadelphia.

Dr. Mastellari served several years as Director of Health, Section on Tuberculosis, Republic of Panama and as Assistant Health Officer for the City of Panama. At the time of his death he was Chief of the Chest Service of the Gorgas Hospital, Professor of Phthisiology of the National University of Panama School of Medicine and Director of the Anti-Tuberculosis Campaign of the Republic of Panama.

Dr. Mastellari occupied a distinguished position in his country and was a member of a great host of medical organizations, including: Fellow, The American Public Health Association, The American Trudeau Society, The American College of Physicians, The American Academy of Allergy; Regent for Central America of the American College of Chest Physicians; Assistant Editor, Journal of Chest Diseases; Member, Pan-American Academy of Medicine and Surgery, National Medical Association of the Republic of Panama, Member and President of the Isthmian Medical Association of the Canal Zone. He was a Corresponding Member of Sociedad Cubana de Tisiologia, Sociedad Chilena de Tisiologia, Sociedad Peruana de Tisiologia, Sociedad Mexicana de Estudios Sobre la Tuberculosis, Sociedad de Lucha Contra la Tuberculosis de Rio Grande del Sud, Sociedad Brasilera de Tuberculosis, Academia de Medicina y Cirugia de Antioquia of Colombia and Sociedad Ecuatoriana de Tuberculosis; Honorary Member, Sociedad de Tisiologia de Venezuela, Sociedad Guatemalteca de Tisiologia, Sociedad Mexicana de Tuberculosis and Sociedad de Tisiologia de Cordoba of Argentina; Member and President, Sociedad Centro Americano de Tisiologia; Technical Advisor in Tuberculosis, Inter-American Service of Public Health.

DR. EDWARD W. McCLOSKEY

On June 16, 1956, Dr. Edward W. McCloskey, F.A.C.P., died at the age of 71 in Philadelphia. Dr. McCloskey was born in the suburbs of Philadelphia in 1885 and spent all of his active life in Philadelphia and its suburbs. He received a B.S. degree from the University of Pennsylvania in 1908 and an M.D. degree from the University of Pennsylvania School of Medicine in 1911. Later he received an honorary M.A. degree from Villanova College and acquired additional postgraduate training at Columbia University. After serving as a resident physician in St. Josephs Hospital in 1911 and 1912, Dr. McCloskey immediately became associated with the Chestnut Hill Hospital which he served most effectively for many years. During the first World War, Dr. McCloskey was an active member of the Medical Reserve Corps, rising from First Lieutenant to Lieutenant Colonel.

In addition to his County and State Societies, he belonged to the American Medical Association and the Philadelphia College of Physicians. He became a

Fellow of the American College of Physicians in 1937.

Dr. McCloskey was known to his patients as "Dr. Ed" to distinguish him from

his brother, Dr. F. McCloskey. During his long career, he numbered among his patients many distinguished persons all of whom had for him a deep affection.

The College extends to his widow, Mrs. Katharine C. R. McCloskey, 7 E. Chestnut Hill Avenue, Philadelphia, Pennsylvania, and to his sister, Sister M. Nicoleta of the Sisters of St. Joseph, its sympathy.

THOMAS M. McMillan, M.D., F.A.C.P., Governor for Eastern Pennsylvania, A.C.P.

DR. MALCOLM CHRISTIAN McCORD

Dr. Malcolm Christian McCord, (Associate), was born at Cincinnati, Ohio, July 10, 1921, and died May 26, 1956, at his home town of Cincinnati. He received his A.B. degree from the University of Michigan in 1942, and his M.D. degree from the University of Michigan Medical School in 1945. He then continued on to receive his M.S. at the University of Colorado Postgraduate School in 1953. Dr. McCord then did postgraduate work at the Veterans Administration Hospital (Dayton, Ohio) the Colorado General Hospital, and the National Heart Institute, after which he served in the Medical Corps of the United States Army from 1946 to 1948, and was discharged with the rank of Captain.

Dr. McCord came to Denver and the University of Colorado School of Medicine on July 1, 1951, and became associated with the Medical School, a position he held until the time of his death. During this time he was also a fellow in the cardio-vascular laboratory from 1951–53. He was promoted to Instructor in the Department of Medicine and would have been further advanced to Assistant Professor of Medicine, effective July 1, 1956. During his five-year period at the Medical School, Dr. McCord maintained a strong interest in both teaching and research activities, and was senior author or co-author of twelve scientific papers during this period. He was a most energetic and effective teacher, and his marked enthusiasm characterized his approach to all problems; largely because of this quality, he was considered one of the finest and most dynamic teachers at the Medical School.

He was a member of the Denver City and County Medical Society, Colorado State Medical Society, American Federation for Clinical Research, American Heart Association, American Medical Association, and a Diplomate of the American Board of Internal Medicine. In 1955, he became an Associate of the American College of Physicians.

Dr. McCord's sudden death on May 26 was a great shock to all of those who had worked closely with him. His death leaves a void in the Department of Medicine that will be difficult, if not impossible, to fill in the manner in which he had performed. His loss will also be particularly felt by the students and others who knew him less intimately, for his great enthusiasm was contagious, and he made an indelible mark on all whom he came into contact with, even though this period may have been a brief one. Dr. McCord is survived by his wife, Mrs. Janet S. McCord, who resides at 120 East Fountain Ave., Glendale, Ohio.

C. F. KEMPER, M.D., F.A.C.P., Governor for Colorado, A.C.P.

DR. JAMES IVAN MOONEY

Dr. James Ivan Mooney, F.A.C.P., died at Rochester, New York, March 28, 1956, after an illness of several months. He was born in Rochester, N. Y., October 3, 1905, and attended both College and Medical School at Syracuse University where

he received his M.D. degree in 1931. After an internship at St. Mary's Hospital in Rochester, he entered private practice. During the succeeding years he received training in the field of allergy and devoted considerable effort to this specialty thereafter in conjunction with his work in internal medicine.

He became an Attending Physician at St. Mary's Hospital where he actively participated in the educational program and where he instituted and directed an allergy clinic. He was also attending physician at the Monroe County Hospital.

Dr. Mooney was a member of the Rochester Academy of Medicine; Rochester Pathological Society; Monroe County Medical Society; American Medical Association; and in 1944 became a Fellow of the American College of Physicians.

Dr. Mooney was a conscientious and capable physician, and his loss is mourned by both his colleagues and his many friends who held him in the highest esteem. He had a remarkable capacity for friendship; and particularly his patients feel his loss most keenly because of his great interest in them personally as well as professionally.

The College extends its sympathy to Dr. Mooney's wife, Genevieve M. Mooney of Rochester, N. Y.

JOHN H. TALBOTT, M.D., F.A.C.P., Governor for Western New York, A.C.P.

DR. PHILIP INGRAM NASH

Dr. Philip Ingram Nash, F.A.C.P., died on April 25, 1956, in Brooklyn, New York.

Dr. Nash was born on July 16, 1875, Cornwall, England. He received the degrees of M.D. and C.M. at Queens University Faculty of Medicine in 1902.

His academic appointments were Clinical Professor of Medicine, Long Island College of Medicine, 1931–37; Emeritus Professor of Clinical Medicine, Long Island College of Medicine, 1937–56.

His hospital appointments were as follows: Attending Physician, 1910–31, Director of Medical Service (1931–46), Consulting Physician (1951–56), Coney Island Hospital; Attending Physician (1919–31), Director of Medical Service (1931–41), Harbor Hospital; Consulting Physician, Madison Park Hospital; Medical Assistant to District Attorney, Kings County; Consulting Physician, Boro Park General and St. Francis Hospitals.

He was a member of the American Medical Association; Medical Society, State of New York; Medical Society, Kings County; Greater New York Medical Society; Associated Physicians of Long Island; Coney Island Medical Society; Brooklyn Pathological Society; New Utrecht Medical Society; American Association for the Advancement of Science; Pan American Medical Society; Diplomate, American Board of Internal Medicine, and Fellow (1924), American College of Physicians.

Dr. Nash is survived by his widow, Mrs. Anna F. Nash, 240 East 18th Street, Brooklyn, New York. His confreres note with sincere regret the passing of Dr. Philip I. Nash.

IRVING S. WRIGHT, M.D., Governor for Eastern New York

DR. RUFUS SARGENT REEVES

On July 13, 1956, Dr. Rufus Sargent Reeves, F.A.C.P., died at his home in Philadelphia at the age of 74, lacking two weeks. Dr. Reeves had had a long and distinguished career and had to his credit sound accomplishments in a number of

phases of medicine. He is probably best known by reason of his having been Director of Public Health of Philadelphia from 1944 to 1952. Many who knew him well will consider his best accomplishment to have been the founding of the Postgraduate Institute of the Philadelphia County Medical Society in 1935. He was distinctly honored by his fellow physicians when he was made President of the Philadelphia County Medical Society in 1939 and given the I. P. Strittmatter Award in 1940.

Dr. Reeves received a B.S. degree from the University of Pennsylvania in 1906 and an M.D. degree from the University of Pennsylvania School of Medicine in 1912. He received his first academic appointment in the University in 1913 and rose through various grades to the position of Associate Professor of Medicine in 1916. The press of other duties forced him to discontinue his active academic career though he found time to accept the position of Lecturer in Public Health, Institute and Local and State Government, University of Pennsylvania, from 1944 to 1952. Dr. Reeves held a number of hospital appointments and had been associated with the Episcopal Hospital, the Methodist Episcopal Hospital, the Mercy-Fitzgerald Hospital, and the Graduate Hospital of the University of Pennsylvania. He was a member of many societies in the field of internal medicine and public health. He became a Fellow of the American College of Physicians in 1938.

The College has lost a distinguished and loyal member and it extends to his wife, Mrs. Emma G. W. Reeves, Presidential Apts., Philadelphia, Pennsylvania, its sincere sympathy.

THOMAS M. McMillan, M.D., F.A.C.P., Governor for Eastern Pennsylvania, A.C.P.

DR. HENRY A. REISMAN

Dr. Henry A. Reisman, F.A.C.P., one of the outstanding pediatricians of Queens County, New York City, died March 30, at Miami Beach, Florida, of acute myocardial infarction. He had retired to his country home at Higganum, Connecticut, only a year before, because of ill health. He was born at New York City on April 12, 1898. He studied at the University of Missouri, where he received his B.A. degree in 1920 and then went to Jefferson Medical College, receiving his M.D. degree in 1922. Dr. Reisman then became affiliated with the New York Postgraduate Medical School and Hospital (1923–40). In 1940 he became Assistant Clinical Professor of Medicine at New York University College of Medicine. He held this post until 1945 when he was appointed Clinical Professor of Pediatrics at New York Medical College Flower and Fifth Avenue Hospitals.

Dr. Reisman, in addition to his academic appointments was actively engaged in the practice of pediatrics (Jamaica, L. I.), for over 30 years. During this time he served as Attending Pediatrician and Director of Pediatrics at Jamaica Hospital. He was the first Visiting Pediatrician at the Queens General Hospital (1935) and later became Director of Pediatrics, a post which he served faithfully and well. Dr. Reisman was a member of the Queens County Medical Society, Brooklyn Pediatric Society, Public Relations and Health Committee of Queens Medical Society and the American Medical Association. He was a Diplomate of the American Board of Pediatrics and a founding member of the Queens Pediatric Society. He was a Fellow of the American Academy of Pediatrics and in 1931 became a Fellow of the American College of Physicians.

Dr. Reisman had earned the respect, admiration and affection of his colleagues and patients, and will be missed by all who knew him.

He is survived by his wife, Mrs. Catharyne T. Reisman, who resides at Little City, Higganum, Connecticut.

JOHN C. LEONARD, M.D., F.A.C.P., A.C.P. Governor for Connecticut

DR. KARL SINGER

Dr. Karl Singer, F.A.C.P., died at Chicago, Illinois, July 12, 1956. He was born at Vienna, Austria, June 9, 1902. He received his M.D. degree in 1927 from the University of Vienna Medical School, and then served his internship and residency in internal medicine at the Francis Joseph Hospital (Vienna), 1927–35.

Dr. Singer was a Visiting Physician at the Poliklinik, Vienna, from 1936–38. He then came to Boston, and was a Research Fellow at the Beth Israel Hospital and the Pratt Diagnostic Clinic from 1938–41. From 1941–47 he served as Assistant Physician at the Boston Dispensary, and later joined the Michael Reese Hospital (Chicago) in 1947 as Director of blood research, a position which he held until his passing.

Dr. Singer carried on his research in problems of the blood with great enthusiasm. He was an energetic teacher, contributing freely to the literature on disorders of the blood through his many papers, monographs, and a book entitled Thrombotic Thrombocytopenic Purpura.

Dr. Singer was a member of the Massachusetts Medical Society, American Medical Association, American Association for the Advancement of Science, Society for Experimental Biology and Medicine, American Society for Human Genetics, International Society of Hematology (Charter Member), American Genetic Association, Chicago Medical Society, Illinois State Medical Society, American Association of Physicians, Central Society for Clinical Research, Chicago Society of Internal Medicine, and a Diplomate of the American Board of Internal Medicine. He becarse a Fellow, in 1953, of the American College of Physicians.

Dr. Singer's friends, relatives, and colleagues deeply mourn the passing of this scholarly gentleman and physician. He is survived by his wife, Mrs. Lily Singer, who resides at 7925 S. Bennett Ave., Chicago 17, Ill.

HOWARD WAKEFIELD, M.D., F.A.C.P., Governor for Northern Illinois, A.C.P.

DR. WILL COOK SPAIN

Dr. Will Cook Spain, F.A.C.P., died on May 12, 1956, in New York City.

Dr. Spain was born on August 10, 1891, at Murfreesboro, Tennessee. He received his Bachelor of Arts degree at the University of Michigan in 1914, and his degree of Doctor of Medicine at Vanderbilt University School of Medicine in 1918. He had postgraduate training at the New York Postgraduate Hospital.

He was Instructor at Cornell Medical School, 1927–34; Instructor, (1925–27), Assistant Professor (1927–32), Associate Professor of Clinical Medicine (1932–37), Professor of Clinical Medicine (1937–56), New York University Postgraduate Medical School.

His hospital appointments were as follows: Attending Physician, Asthma Clinic, 1920–26; Chief of Asthma Clinic, 1926–28, New York City Hospital; Associate Attending Physician and Chief of the Allergy Clinic, 1925–37; Attending Physician and Chief of the Department of Allergy, 1937–56, New York University-Bellevue

Medical Center Hospital; Visiting and Attending Physician at the various medical divisions of the New York University-Bellevue Medical Center since 1930.

Dr. Spain was a member of the New York Academy of Medicine; New York State Medical Society; American Medical Association; American Association of Immunologists; Society for the Study of Asthma and Allied Conditions (Secretary-Treasurer, 1925–45); Phi Chi (Medical Fraternity); American Academy of Allergy, Secretary, 1944, Vice President, 1946, and President, 1947; Pan American Medical Association, President, Section on Allergy, 1952–53; Member of the Editorial Board of the Journal of Allergy, The American Academy of Medicine, 1953–56; Diplomate, the American Board of Internal Medicine (Specialty, Allergy); Fellow (1938) of the American College of Physicians, and Alpha Omega Alpha.

He served as a First Lieutenant in the United States Army Medical Corps during the First World War.

Dr. Spain did very extensive writing in his field of specialization and many of his articles were published in the leading medical journals.

He is survived by his widow, Mrs. Will Cook Spain, 375 Park Avenue, New York.

Dr. Spain made a great and lasting contribution by the training of many physicians in the science of allergy. His loss will be deeply felt by his many close friends and students.

IRVING S. WRIGHT, M.D., F.A.C.P., Governor for Eastern New York

DR. FRED LELAND WEBB

Dr. Fred Leland Webb, F.A.C.P., of Nashville, Tennessee, was born on February 18, 1873, at Boone, Iowa. He grew up in that State and was educated there, receiving his A.B. degree at Iowa State College, in 1896. After a brief period in business he entered the Jefferson Medical College of Philadelphia, receiving his M.D. degree in 1902. He was on the house staff of the Methodist Episcopal Hospital in Philadelphia from 1902 to 1904, and following a brief period of practice in Waterloo, Iowa, entered practice in Macon, Georgia, where he lived until 1933, when he gave up his active practice. During these years he was Senior Internist of the Macon Hospital and took an active part in the affairs of this institution.

During World War I he entered the Army in May of 1917 and was discharged as a Major in October, 1919. Having maintained his commission as Major in the Reserve Corps of the United States Army, upon retiring from practice in 1933, he went on active duty as a Major at Fort Oglethorpe, Georgia, first as Internist and then Attending Surgeon of the Station Hospital. He then became Assistant District Surgeon for the C.C.C. During the first year of World War II he examined recruits and inductees at the Induction Center at Fort Oglethorpe.

Upon his retirement he joined the Nashville City Health Department as a Senior Medical Officer in the Venereal Disease Control Program, continuing this activity until 1953. In two years subsequent to this Dr. Webb was part-time physician to the Blood Bank Foundation of Nashville.

Dr. Webb was an Episcopalian, took an active part in the Shrine, of which he was a member since 1913, and was always a member of organized medicine. In the Macon Medical Society he was Secretary in 1910, Treasurer in 1911, Vice President in 1912, and President in 1913. He was Vice President of the Medical Association of Georgia in 1920 and President in 1926. He held membership in the American Medical Association, the Southern Medical Association, and joined the Tennessee State Medical Association upon moving to this State. He was a member

of the Alpha Kappa Kappa Medical Fraternity. He became a Fellow of the American College of Physicians in 1931.

He had postgraduate training at Cook County Hospital, Chicago, in the U. S. Army Training School and in Venereal Disease Control at Vanderbilt University School of Medicine.

To the last Dr. Webb was a consistent reader of current medical literature, and in conversation with him one was always aware of his knowledge of the recent advances in medicine. He liked people, and those who observed him in the Venereal Disease Clinic were aware of the kindly humor with which he handled this group of people.

Dr. Webb died on March 26, 1956, in Nashville, of coronary occlusion, at the age of 83 years. He is survived by his wife, Ruby Rowland Webb of Nashville, and a daughter, Alice Webb Sloane of Washington, D. C.

R. H. KAMPMEIER, M.D., F.A.C.P., Governor for Tennessee

CAPTAIN OTIS WILDMAN

Captain Otis Wildman, F.A.C.P., died at the U. S. Naval Hospital, Bethesda, Maryland, May 14, 1956, aged 65, of myocardial infarction.

Dr. Otis Wildman was born in Jennings County, Indiana, September 13, 1890. He received his B.S. degree in 1915 and his M.D. degree in 1917 from the University of Indiana. It is apparent that he immediately entered the U. S. Naval Medical Service at that time and spent some months in the U. S. Naval Medical School and pursued some special study at the Rockefeller Institute for Medical Research. His field of special interest was Pathology and Clinical Pathology. He filled many successive assignments in various departments of the Medical Corps of the Navy and rose to the rank of Captain. He was certified by the American Board of Pathology and was the author of a goodly list of published papers in his field. He retired from active service November 1, 1943 and had resided thereafter in Washington, D. C.

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1. Welch, H.: Antibiotic Med. 2:11 (Jan.) 1956.

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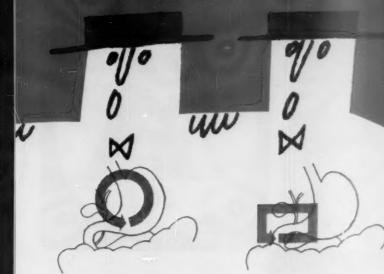
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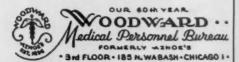
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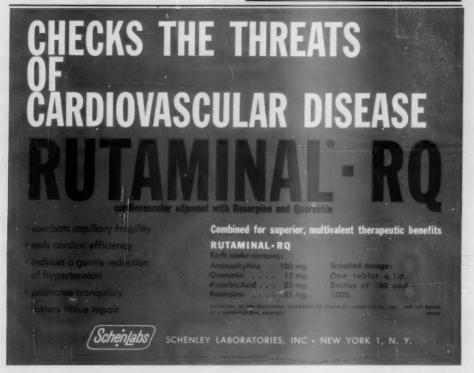
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 Schwartz, J.: Am. J. Obst. 63:1069, 1952.
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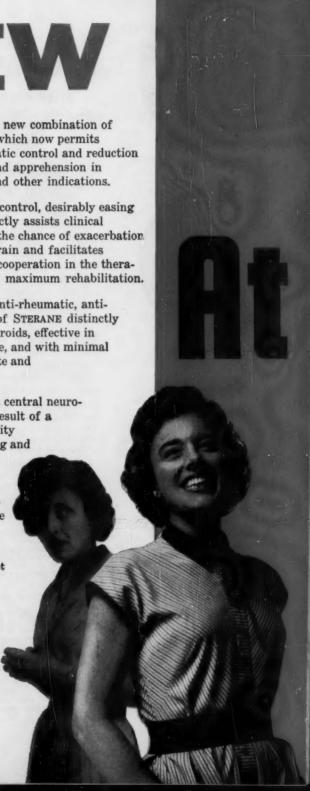
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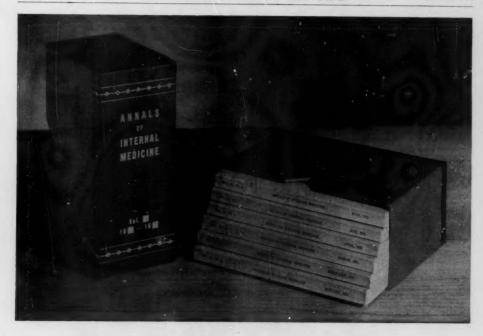
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- Sturnick, M. I.; Riseman, J. E. F.; and Sagall, E. I.: Studies on the Action of Quinidine in Man: J. A. M. A. 121; 917 (March 20) 1943
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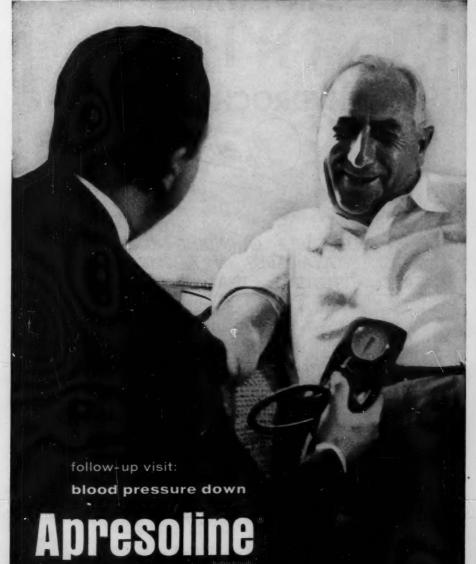
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